

ASHP Therapeutic Guidelines on the Pharmacologic Management of Nausea and Vomiting in Adult and Pediatric Patients Receiving Chemotherapy or Radiation Therapy or Undergoing Surgery

These therapeutic guidelines are intended to assist health care professionals in the appropriate management of adult and pediatric patients with nausea and vomiting induced by chemotherapeutic agents, radiation therapy, or surgery. There has been a renewed interest in the treatment of nausea and vomiting based on an improved understanding of the physiologic mechanisms involved in emesis. This interest has led to a continued proliferation of clinical trials of antiemetic therapies. Mild cases of nausea or vomiting may be disconcerting, but frequently symptoms are self-limiting and treatment can be simple and inexpensive. More severe nausea and vomiting can result in dehydration, malnutrition, and metabolic disturbances, which can have a substantial effect on quality of life, survival, and health care costs. Even mild nausea and vomiting may have late sequelae, such as anticipatory emesis in patients receiving chemotherapy. Therefore, primary prevention of nausea and vomiting is paramount.

The availability of new antiemetic agents and formulations has raised questions about the most cost-effective way to manage nausea and vomiting. Antiemetic therapy was selected for guideline development because (1) nausea and vomiting occur frequently, (2) there is a lack of consistency in selection of therapeutic agents in clinical practice, and (3) nausea and vomiting are preventable, which means there is potential for a significant impact on clinical, humanistic, and economic outcomes.

Nausea, vomiting, and retching are three separate entities that are assessed independently. Nausea is a subjectively unpleasant sensation associated with flushing, tachycardia, and an awareness of the urge to vomit. Vomiting, or emesis, is characterized by contraction of the abdominal muscles, descent of the diaphragm, and opening of the gastric cardia, resulting in expulsion of stomach contents from the mouth. Retching involves spasmodic contractions of the diaphragm, thoracic, and abdominal wall muscles without expulsion of gastric contents. Many medications, medical conditions, and procedures have been shown to induce nausea and vomiting (Table 1).

As a drug class, chemotherapeutic agents frequently induce nausea and vomiting; however, not all of these agents have the same propensity to induce symptoms. In the absence of antiemetic agents, vincristine is associated with nausea and vomiting in less than 10% of patients while cisplatin induces these symptoms in more than 90% of patients.¹ In one study, vomiting occurred in 47 (98%) of 48 patients receiving cisplatin without antiemetic therapy.⁴ Patients had a median of six emetic episodes in the first 24 hours after administration of cisplatin. Vomiting continued after rescue therapy with antiemetics in 77% of patients during this 24-hour period.

The frequency of postoperative nausea and vomiting is influenced by the surgical procedure, the age and sex of the patient, and other medications administered, but the overall frequency, defined by large-scale clinical trials, has been estimated to be 20–30%.⁵⁻⁷

Radiation therapy, with or without concomitant chemotherapy, has also been shown to induce nausea and vomiting. Nausea and vomiting occur most commonly when the gastrointestinal (GI) tract is irradiated. It has been estimated that more than 80% of patients receiving mid- and upper-hemibody radiation experience nausea and vomiting.⁸⁻¹² Specific factors that increase the risk of nausea and vomiting with chemotherapy, radiation therapy, or surgery are addressed in a subsequent section of this document.

Hundreds of studies have assessed the effect of pharmacologic therapy on nausea and vomiting associated with precipitating factors; however, the quality of the literature varies significantly.¹³⁻¹⁶ Methodological concerns with published antiemetic trials that make comparisons between treatment options difficult include the following^{13,15,16}:

- Inclusion of heterogeneous patient populations (e.g., selection of patients receiving chemotherapeutic agents with differing levels of emetogenicity or patients undergoing differing types of surgery).
- Use of a variety of doses, routes of administration, schedules, and combinations of antiemetic agents.
- Lack of randomization.
- Inadequate blinding of investigators or patients to study medications.
- Rarity of placebo controls (primarily because of ethical considerations).
- Insufficient sample size to provide enough power to detect a difference between study groups if there was a true difference.
- Inadequate assessment of nausea, vomiting, and retching, including what was measured, who performed the assessment, and scales of measurement.
- Inconsistent definition of successful treatment.
- Rarity of outcomes data, including humanistic, economic, and other clinical outcomes (e.g., adverse effects of medications).

Several reviews discuss this topic more extensively.¹³⁻¹⁶

Nausea and vomiting can potentially affect large numbers of patients; however, current evidence suggests a lack of consistency in the management of these symptoms in clinical practice.^{1-3,5-7,13,17-20} Pharmacologic management should be based on systematic evaluation of currently available scientific evidence and on medication-specific and patient-specific variables, including the type of emetic stimulus; the ability and willingness of patients to use oral, rectal, or injectable medications; prior alcohol use; age; concomitant diseases or medications; the frequency, duration, and severity of symptoms; sex; the success of previous treatment; suspected cause and precipitating factors; and patient preference.

Adverse effects of antiemetics also need to be considered when specific agents are selected. Table 2 lists common adverse effects of antiemetic agents.

Antiemetic agents are most useful when given prophylactically; it is much easier to prevent symptoms than to control them. When preventive measures are successful, adverse clinical, humanistic, and economic outcomes can be avoided.

Severe or protracted nausea and vomiting can result in dehydration, malnutrition, metabolic disturbances (e.g., metabolic alkalosis, hyponatremia, hypochloremia, and hypokalemia), and aspiration pneumonia.^{3,21,22} These complications can be life threatening; infants and children are at particularly high risk. The pressure generated by vomiting can cause rupture of the esophagus (Boerhaave's syndrome) or linear mucosal tears (Mallory-Weiss syndrome) in the region of the cardioesophageal junction, with resulting hematemesis. Patients receiving chemotherapy may be unable to tolerate subsequent courses of chemotherapy, or the symptoms may be so severe that the patient refuses further cycles of chemotherapy.^{19,21}

The effects of uncontrolled nausea and vomiting on quality of life are also an important consideration.^{20,23-26} Much of the research assessing quality-of-life implications of nausea and vomiting relates to patients receiving cancer chemotherapy. Studies have shown that nausea and vomiting secondary to chemotherapy reduce the patient's ability to complete household tasks, enjoy meals, spend time with others, and maintain activities of daily living and recreation.^{24,25} Nausea and vomiting can be so distressing that patients may be unable to work, care for themselves, or take their prescribed medications. Vomiting seems to have a greater impact on daily functioning than nausea.

The Functional Living Index—Cancer (FLIC) and the Functional Living Index—Emesis (FLIE) are two instruments used in research to evaluate the impact of chemotherapy-induced nausea and vomiting on quality of life. The FLIE contains nine items for assessing nausea and another nine for vomiting and addresses the effect of nausea and vomiting on physical activities, social and emotional function, and the ability to enjoy meals. The possible score ranges from 18 to 126, with lower scores indicating a more negative impact on the patient's functional living as a result of nausea and vomiting. Lindley and colleagues²⁴ demonstrated a significant and dramatic decline in the quality of life of outpatients receiving chemotherapy by using the FLIE. The mean FLIE score decreased from 115 immediately before chemotherapy to 85 three days after chemotherapy in patients with emesis. This study also showed cost-related consequences of chemotherapy-induced emesis: 23% of patients missed work, 22% were unable to prepare meals, 12% were unable to take care of themselves, and 12% were unable to take prescribed medications on at least one occasion. The economic significance was not assessed but warrants further study.²⁴

More recently, Osoba and colleagues²⁶ used a health-related quality of life (HQL) questionnaire to assess symptoms in chemotherapy-naïve patients who received either moderately or highly emetogenic chemotherapy. This study showed significant worsening of scores in cognitive function, global quality of life, fatigue, anorexia, insomnia, and dyspnea in patients who vomited compared with those who did not vomit within seven days after chemotherapy. The study also indicated that global quality of life, physical function, role function, social function, fatigue, and anorexia were significantly worse before chemotherapy in patients who subsequently vomited than in those who did not vomit. This suggests that HQL scores may have value in

Table 1.
Classes of Drugs, Medical Conditions, and Procedures That May Induce Nausea and Vomiting¹⁻³

<i>Drug or Drug Class</i>	
Anesthetic agents (e.g., thiopental, halothane)	
Antidepressants (e.g., fluoxetine, sertraline, paroxetine, fluvoxamine)	
Antimicrobials (e.g., imipenem–cilastatin, erythromycin, vancomycin, metronidazole, trimethoprim–sulfamethoxazole, nitrofurantoin)	
Antifungals (e.g., itraconazole)	
Contrast media	
Corticosteroids	
Cytotoxic agents (e.g., cisplatin, cyclophosphamide)	
Ergot alkaloids (e.g., dihydroergotamine, ergotamine, methysergide, pergolide)	
Estrogen-containing substances	
Iron formulations (e.g., iron dextran, ferrous gluconate, ferrous fumarate, ferrous sulfate, ferrous phosphate)	
Levodopa and carbidopa	
Nonsteroidal anti-inflammatory drugs	
Opioids (e.g., morphine, fentanyl)	
Potassium salts (e.g., acetate, phosphate, chloride [oral more than i.v.], gluconate)	
Tramadol	
<i>Medical Condition or Procedure</i>	
Anxiety	
Cerebral metastases	
Gastrointestinal malignancies	
Hepatitis	
Hypercalcemia	
Hepatic metastases	
Intestinal obstruction	
Migraine headaches	
Morning sickness and hyperemesis gravidarum	
Motion sickness	
Menière's disease	
Motility disorders (e.g., gastroparesis, irritable bowel syndrome)	
Pain	
Pancreatitis	
Peritonitis	
Renal colic	
Radiation therapy	
Surgery	

predicting which patients might experience chemotherapy-induced emesis and thus require additional antiemetic strategies for adequate emesis control.

The choice of antiemetic agent may affect resource use and costs. An inappropriate agent or dose may result in increases in cost associated with rescue therapy or wasted drug (e.g., 32 mg of ondansetron when 8 mg would have sufficed), nursing time, cleanup time, emergency room or clinic visits, hospital admission, or complicated and extended hospital stay. These types of issues, in addition to patient satisfaction, may ultimately affect managed care contracts.

Scope

These guidelines address the management of adult and pediatric patients with nausea and vomiting induced by chemotherapeutic agents, radiation therapy, or surgery. The guidelines were written to be applicable to both the inpatient and outpatient setting. Management of populations at risk of nausea and vomiting associated with other medications, procedures, or medical conditions are not within the scope of this document. Nonpharmacologic strategies such as music therapy, hypnosis, progressive muscle relaxation, diversion therapy, guided imagery, biofeedback, self-hypnosis, di-

etary modifications, and acupuncture may be valuable adjuvants but are beyond the scope of this document.²⁷⁻³² Some standard regimens could not be incorporated into the guidelines because of a lack of randomized clinical trials. The guidelines should not be routinely applied to patients with a relative contraindication to any of the agents recommended.

Guideline Development and Use

The ASHP Therapeutic Guidelines on the Pharmacologic Management of Nausea and Vomiting in Adult and Pediatric Patients Receiving Chemotherapy or Radiation Therapy or Undergoing Surgery were prepared by the University of Kentucky Drug Information Center under contract to ASHP. The project was coordinated by the director of the center, who worked in conjunction with an independent panel of seven clinical specialists (a physician, a nurse, and five pharmacists) representing adult and pediatric hematology–oncology and surgery–anesthesia. The panel was appointed by ASHP. Panel members and contractors were required to disclose any possible conflicts of interest before appointment.

The scientific literature is the foundation for the recommendations. A comprehensive literature search was performed. Published studies identified through a MEDLINE search (1966 to April 1998) were reviewed, as were the reference lists of the retrieved documents and abstracts from meetings of professional associations, when appropriate. The literature was critically evaluated, including examination of research design, patient selection, medication dose, route, combination treatment, test measures, statistics, and results. Recommendations were graded A, B, C, or D according to the strength of scientific evidence:

- A.** Strong research-based evidence (multiple relevant and high-quality scientific studies),
- B.** Moderate research-based evidence (one relevant, high-quality scientific study or multiple adequate scientific studies),
- C.** Limited research-based evidence (at least one adequate scientific study in patients with nausea and vomiting, published in a reputable medical journal), and
- D.** Panel interpretation of information that did not meet inclusion criteria as research-based evidence.

The same system was previously used by an AHCPR panel of experts to develop guidelines.³³ The strength of evidence appears in parentheses after the recommendation and reflects both the overall quality of the studies and the strength of the study design.

The primary clinical endpoint that was considered as the definition of complete response in the studies was the number of patients with no vomiting episodes. Secondary endpoints included the number of patients with no nausea or retching and documentation of reduction in the number of emetic episodes or the severity of nausea. Clinical trials describing pharmacologic management that influenced humanistic or economic outcomes were strongly considered.

A panel of experts was created to ensure that applicable studies were included in the analysis, to provide expert judgment when the literature was of poor quality or lacking, and to provide insight into the clarity, practicality, and flexibility of the document in clinical practice. The guidelines were circulated in draft form, and all members of the panel had the opportunity to comment on the recommenda-

Table 2.
Adverse Effects of Antiemetic Agents

Medication	Adverse Effects ^a
<i>Antihistamines</i> Diphenhydramine, hydroxyzine	Most common: sedation, dry mouth, constipation; less common: confusion, blurred vision, urinary retention
<i>Belladonna alkaloid</i> Scopolamine	Most common: dry mouth, drowsiness, impaired eye accommodation; rare: disorientation, memory disturbances, dizziness, hallucinations
<i>Benzamides</i> Benzquinamide, metoclopramide, trimethobenzamide	Most common: sedation, restlessness, diarrhea (metoclopramide), agitation, central nervous system depression; less common: extrapyramidal effects (more frequent with higher doses), hypotension, neuroleptic syndrome, supraventricular tachycardia (with i.v. administration)
<i>Benzodiazepines</i> Lorazepam	Most common: sedation, amnesia; rare: respiratory depression, ataxia, blurred vision, hallucinations, paradoxical reactions (weeping, emotional reactions)
<i>Butyrophenones</i> Droperidol, haloperidol	Most common: sedation, hypotension, tachycardia; less common: extrapyramidal effects, dizziness, increase in blood pressure, chills, hallucinations
<i>Cannabinoids</i> Dronabinol	Most common: drowsiness, euphoria, somnolence, vasodilation, vision difficulties, abnormal thinking, dysphoria; less common: diarrhea, flushing, tremor, myalgia
<i>Corticosteroids</i> Dexamethasone, methylprednisolone	Most common: gastrointestinal upset, anxiety, insomnia; less common: hyperglycemia, facial flushing, euphoria, perineal itching or burning (with dexamethasone, probably secondary to vehicle and rate of injection)
<i>Phenothiazines</i> Prochlorperazine, promethazine, chlorpromazine, triethylperazine	Most common: sedation, lethargy, skin sensitization; less common: cardiovascular effects, extrapyramidal effects, cholestatic jaundice, hyperprolactinemia; rare: neuroleptic malignant syndrome, hematologic abnormalities
<i>Serotonin Antagonists</i> Ondansetron, granisetron, dolasetron	Most common: headache, asymptomatic prolongation of electrocardiographic interval; less common: constipation, asthenia, somnolence, diarrhea, fever, tremor or twitching, ataxia, lightheadedness, dizziness, nervousness, thirst, muscle pain, warm or flushing sensation on i.v. administration; rare: transient elevations in serum transaminases

^aMost common = >10%, less common = 1–10%, rare = <1%. Based on FDA-approved labeling and generalized to the drug class.

tions and strengths of evidence. The guidelines underwent multidisciplinary field review to evaluate their validity, reliability, and utility in clinical practice. The final document was approved by the ASHP Commission on Therapeutics and the ASHP Board of Directors. The guidelines are scheduled for review and update in two to four years.

The recommendations in this document may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgment of the clinician, individual patient circumstances, and available resources.

Assessment of Nausea and Vomiting

The goal of prophylaxis and treatment is to either alleviate or minimize nausea and vomiting, depending on patient-specific and causative factors (e.g., operative procedure, cytotoxic agent). Nausea and vomiting should be considered as two separate entities and should be assessed as such. The severity and duration of nausea and the number of episodes and duration of vomiting and retching are important considerations. Systematically documenting nausea and vomiting provides the basis for adjusting the medication to suit the individual patient's needs—adjusting the antiemetic dose or dosage interval, providing scheduled doses of antiemetics, adding an as-needed antiemetic agent for breakthrough nausea and vomiting, or changing the route of administration. When nausea and vomiting are being assessed, it is important to select a clinically justified time frame for measuring changes.

Methods for assessing nausea and vomiting¹⁴ are well established for chemotherapy-induced nausea and vomiting; however, they are described to a lesser extent for radiation therapy-induced and postoperative nausea and vomiting. Methods as simple as specifying present or absent or yes or no have been used, as have 3-point, 4-point, 5-point, 6-point, and 10-point scales. Visual-analogue scales are another alternative. Regardless of the method used, it is important for the patient to perform the assessment instead of relying on the perception of the caregiver.

The visual-analogue scale, which is used to quantify the intensity of nausea on a 100-mm line with two extremes, can be vertical (with 100 mm representing severe symptoms on the top and 0 mm representing the absence of symptoms on the bottom) or horizontal.³⁴ This instrument may be particularly beneficial for patients with sight impairment or a low level of literacy. The scale can be altered for children, with a smiling face at the top and a frowning face on the bottom. Patients are asked to mark the scale at a point that best indicates the sensation at the time. The measurement should be taken at the most likely time of nausea or at regular intervals. It is recommended that, if feasible, the patient be seated at the time of measurement rather than remaining supine, in order to more accurately assess the intensity.³⁵ The four-point scale has also been frequently used and is preferred by some because of its simplicity.¹⁴ Nausea is graded by the patient as “none,” “mild,” “moderate,” or “severe.”

Vomiting and retching are assessed separately from nausea; this assessment should be done in an objective manner. Retching needs to be clearly differentiated from vomiting. The number and duration of episodes should be recorded over a 24-hour period. If chemotherapy is being administered, antiemetic efficacy should also be evaluated between courses. Patients should be interviewed about control of nausea and vomiting.

Patients should be monitored for the occurrence of adverse effects, adherence to treatment, hydration status, food intake, and wound dehiscence if applicable. Adverse effects of the antiemetics should also be monitored (Table 2), as should the ramifications of uncontrolled nausea and vomiting (e.g., electrolyte disturbances, dehydration). The overall period for which the patient needs to be assessed depends on patient-specific and causative factors.

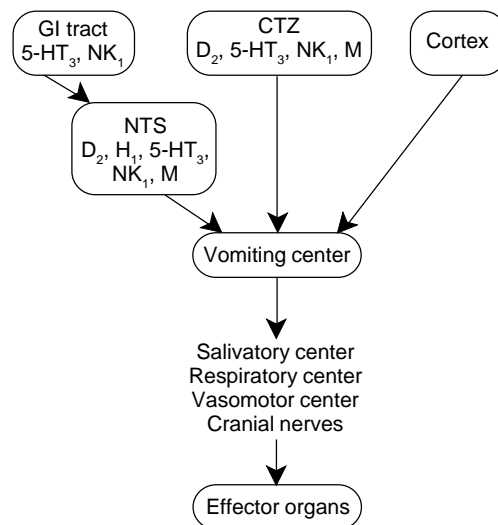
Physiology of Chemotherapy-Induced Nausea and Vomiting

The mechanism of chemotherapy-induced nausea and vomiting is a complex interaction between neurotransmitters and receptors in the central and peripheral nervous systems (Figure 1). The process is initiated by the stimulation of dopamine, opiate, histamine, acetylcholine, neurokinin 1 (NK₁) or serotonin receptors. Dopamine type 2 and serotonin type 3 (5-HT₃) receptors seem to be the most important in chemotherapy-induced nausea and vomiting.

There has been a vast amount of research on the role of serotonin in this process. Both cancer chemotherapy and radiation therapy are known to induce emesis at least in part by causing enterochromaffin cells lining the GI tract to release serotonin.³⁶⁻³⁸ The serotonin binds to vagal afferent 5-HT₃ receptors in the GI tract, which send impulses to the vomiting center located in the lateral reticular formation of the medulla in the brain. The vomiting center is a physiological rather than an anatomic entity, consisting of intertwined neural networks in the nucleus tractus solitarius of the medulla oblongata. The vomiting center also receives impulses from the chemoreceptor trigger zone (CTZ), the brain cortex, and the vestibular apparatus.

The CTZ is considered to play an important role in chemotherapy-induced emesis. The CTZ is located in the area postrema, in the floor of the fourth ventricle. It lies outside the blood-brain barrier where it is accessible to

Figure 1. Pathways and neurotransmitter receptors in chemotherapy-induced nausea and vomiting. GI = gastrointestinal, CTZ = chemoreceptor trigger zone, NTS = nucleus tractus solitarius, D₂ = dopamine type 2 receptor, 5-HT₃ = serotonin type 3 receptor, M = muscarinic receptor, H₁ = histamine type 1 receptor, NK₁ = tachykinin neurokinin type 1 receptor.



circulating emetogenic substances (e.g., chemotherapeutic agents) in both the blood and the cerebrospinal fluid. This location is important because most chemotherapeutic agents do not cross the blood–brain barrier. The CTZ sends impulses to the vomiting center, which in turn initiates the vomiting cascade by sending efferent impulses to the respiratory, vasomotor, and salivary centers and to cranial nerves VIII and X. Subsequently, impulses are sent to the abdominal muscles, the diaphragm, the stomach, and the esophagus, ultimately resulting in emesis.

The influence of the limbic system on the emetic response is less well understood. The limbic region of the brain, within the cerebral cortex, initiates emesis from chemotherapy indirectly. This region of the brain is responsible for anticipatory or learned responses, which is important if nausea and vomiting are not adequately controlled during a patient's initial course of chemotherapy. This process relates more to the psychological components of nausea and vomiting than to those causing direct stimulation.

Acute Versus Delayed Nausea and Vomiting. Chemotherapy-induced nausea and vomiting can be divided into three distinct types: acute, delayed, and anticipatory. Traditionally, acute nausea or vomiting is defined as that occurring within the first 24 hours after administration of cancer chemotherapy. Delayed nausea or vomiting is defined as that beginning at least 24 hours after administration of cancer chemotherapy; it may last for longer than 120 hours. In placebo-controlled trials reported by Gralla et al.,³⁹ Homesley et al.,⁴⁰ Cubeddu et al.,⁴¹ and Cupissol et al.,⁴² 98% of patients receiving cisplatin at doses of 50–120 mg/m² had emesis within 24 hours after the dose. Kris et al.⁴³ described the frequency and severity of symptoms 24–144 hours after administration of cisplatin. Symptoms were greatest 48–72 hours after cisplatin therapy. Some 61% of patients had delayed emesis, with a median number of emetic episodes of two per patient; 78% of patients had delayed nausea. DeMulder and colleagues⁴⁴ studied a group of patients receiving cisplatin 50–100 mg/m² and observed delayed emesis in 62% of patients given oral metoclopramide and 65% of patients given oral ondansetron over a five-day period.

Delayed emesis has also been described in patients receiving less emetogenic doses of cisplatin and in patients receiving combinations containing an anthracycline plus cyclophosphamide. There are no placebo-controlled trials quantifying delayed emesis among patients receiving cyclophosphamide and doxorubicin combinations at various dosages. However, Schmoll⁴⁵ demonstrated that the frequency of delayed vomiting among patients given either metoclopramide or ondansetron was 34% and 17%, respectively, during the 24–48 hours after chemotherapy and 16% and 11%, respectively, during the 48–72 hours after chemotherapy. Jones et al.⁴⁶ noted delayed emesis for up to 120 hours after administration of cyclophosphamide and anthracycline combinations despite treatment with either dexamethasone or ondansetron.

The time frame of 24 hours as the definition of delayed as opposed to acute was arbitrarily assigned. However, when the course of vomiting was examined over the 24 hours after administration of cisplatin 120 mg/m², two vomiting peaks were noted—one at approximately 4 hours and one at 18 hours—with virtually no vomiting between those times.^{4,39,47} High-dose metoclopramide and ondansetron attenuated the first peak, but neither eliminated or attenuated the second peak. When serotonin metabolites (5-hydroxyindolacetic

acid, or 5-HIAA) are measured in the urine after high-dose cisplatin therapy, a peak is found at 6 hours but not at 48 hours.⁴⁸ This suggests that serotonin is not the primary mediator of symptoms for delayed emesis and is confirmed by the lower efficacy rate of ondansetron for preventing delayed emesis than for preventing acute emesis.^{44,49,50} These observations of the pattern of emesis after high-dose cisplatin suggest that delayed emesis may begin as early as 16 hours after chemotherapy.

The pattern of emesis after administration of high-dose cyclophosphamide differs from the time course of emesis induced by cisplatin. Cyclophosphamide is associated with a more prolonged pattern of emesis, demonstrating a latency period of approximately 10 hours, after which nausea and vomiting begin and continue for up to three days.⁴⁴ Reasons for the latency period are unclear, but data suggest that conversion of cyclophosphamide to active metabolites may be required. There is little or no elevation of urinary 5-HIAA in patients given high doses of cyclophosphamide.⁴⁴ This may be because cyclophosphamide induces less serotonin release from enterochromaffin cells than cisplatin does, which may account for the less severe emesis produced by cyclophosphamide. Serotonin antagonists have not demonstrated superiority over dexamethasone with or without metoclopramide in treating delayed emesis after cyclophosphamide-based chemotherapy.^{45,46} This lends further support to the hypothesis that delayed emesis may begin at less than 24 hours and that additional neurophysiological mechanisms may be involved.

Breakthrough Nausea and Vomiting. Breakthrough nausea and vomiting are nausea and vomiting that occur despite preventive therapy. Antiemetic treatment administered to patients who have not responded to prophylactic regimens prescribed for acute or delayed nausea and vomiting is often referred to as rescue therapy.

Anticipatory Vomiting. Anticipatory vomiting is defined as a learned or conditioned response typically occurring when nausea and vomiting have been controlled poorly by previous administration of chemotherapy.⁶ It occurs before, during, or after the administration of chemotherapy but before acute chemotherapy-related symptoms would be expected to occur. Anticipatory nausea and vomiting are not controlled by antiemetic agents or other pharmacologic interventions but have been treatable through behavioral modification and other nonpharmacologic approaches. Behavioral interventions may be effective because they produce physiological relaxation, divert attention away from the conditional stimulus and toward neutral or relaxing images, and enhance feelings of control.^{51–53} Although reports suggest that the amnesic and anxiolytic properties of lorazepam may help prevent anticipatory nausea and vomiting by blocking the memory of emesis associated with chemotherapy, this has not been substantiated by large, randomized trials.^{54–56} Efforts should be directed at preventing nausea and vomiting by administering the most effective antiemetic with the initial course of emesis-producing chemotherapy.

Factors to Consider in the Selection of an Agent for Chemotherapy-Induced Nausea and Vomiting

Because no single agent is completely effective (i.e., resulting in the absence of nausea and vomiting) in all patients,

individualization of therapy is important. Considerations in the selection of an agent for the prevention and treatment of nausea and vomiting include the type, dose, and schedule of chemotherapy; the type of symptoms (acute or delayed); the outcome of previous therapy; anticipated adverse effects (Table 2); the frequency and severity of nausea and vomiting; and patient preference.

The primary factor that influences the frequency and severity of chemotherapy-induced nausea and vomiting is the emetic potential of the cytotoxic agent (Table 3). For most chemotherapeutic agents (e.g., cisplatin), higher doses are more emetogenic than lower doses (Table 4).^{6,13,21,58-62} Slowing the infusion rate by prolonging the infusion time may decrease the risk of emesis. For example, increasing the infusion time of cisplatin from one hour to eight hours resulted in a small but significant reduction in emesis.⁵⁸

Patient-specific factors also affect the risk of nausea and vomiting (Table 4).^{6,13,21,58-62} Patients younger than 50 years have more nausea and vomiting than older patients. Because they have greater physiological reserves, younger patients may receive more aggressive chemotherapy, leading to more nausea and vomiting. Women are more susceptible to nausea and vomiting than men.⁶ Limited evidence suggests that people who have had motion sickness or pregnancy-related nausea and vomiting may be more apt to have problems with chemotherapy. Patients who use alcohol heavily or who have done so in the past have a reduced risk of emesis. Patients who have vomited repeatedly after prior doses of chemotherapy are more likely to have nausea and

vomiting with subsequent doses.¹³

Knowledge of the patterns of emesis after administration of specific chemotherapeutic agents aids in the selection of antiemetic agents and dosage schedules that will allow for adequate protection at the expected time of onset and for the duration of both acute and delayed nausea and vomiting.⁶³ Table 5 shows the expected onset and duration of emesis for commonly used chemotherapeutic agents.^{16,63-66}

Mechlorethamine induces emesis within 30 minutes after intravenous administration, whereas other agents with very high emetic potential (e.g., cisplatin, dacarbazine, streptozocin) usually do not induce emesis for at least one hour after administration. With moderately emetogenic agents (e.g., daunorubicin, doxorubicin, ifosfamide), emesis often develops within six hours.⁶³ A later onset of acute emesis occurs with certain agents, particularly cyclophosphamide. This variability in occurrence and onset suggests that individual drugs may cause emesis by different mechanisms and that some agents (e.g., cyclophosphamide) require metabolic activation to cause emesis, delaying the onset.⁶⁴

The duration of emesis also is agent dependent. Most chemotherapeutic drugs can cause emesis for approximately 12–24 hours after administration. Two exceptions are cisplatin, with a duration of emesis of more than 24 hours, and cyclophosphamide, with a duration of 6–36 hours.

The rate of drug administration affects the onset, intensity, and duration of chemotherapy-induced emesis. The occurrence of emesis after a continuous infusion typically peaks within the first day of treatment and gradually

Table 3.
Emetogenicity of Chemotherapeutic Agents^{57,a}

<i>Level 1 (Less Than a 10% Frequency)</i>	<i>Level 3 (30–60% Frequency)</i>
Androgens	Aldesleukin ^c
Bleomycin	Cyclophosphamide (i.v., ≤750 mg/m ²)
Busulfan (oral, <4 mg/kg/day)	Dactinomycin (≤1.5 mg/m ²)
Chlorambucil (oral)	Doxorubicin hydrochloride (20–60 mg/m ²)
Cladribine	Epirubicin hydrochloride (≤90 mg/m ²)
Corticosteroids	Idarubicin
Fludarabine	Ifosfamide
Hydroxyurea	Methenamine (oral)
Interferon	Methotrexate (250–1000 mg/m ²)
Melphalan (oral)	Mitoxantrone (≤15 mg/m ²)
Mercaptopurine	<i>Level 4 (60–90% Frequency)</i>
Methotrexate (≤50 mg/m ²) ^b	Carboplatin
Thioguanine (oral)	Carmustine (<250 mg/m ²)
Tretinoin	Cisplatin (<50 mg/m ²)
Vinblastine	Cyclophosphamide (>750 mg/m ² to ≤1500 mg/m ²)
Vincristine	Cytarabine (≥1 g/m ²)
Vinorelbine	Dactinomycin (>1.5 mg/m ²)
<i>Level 2 (10–30% Frequency)</i>	Doxorubicin hydrochloride (>60 mg/m ²)
Asparaginase	Irinotecan
Cytarabine (<1 g/m ²) ^b	Melphalan (i.v.)
Docetaxel	Methotrexate (≥1000 mg/m ²)
Doxorubicin hydrochloride (<20 mg/m ²)	Mitoxantrone (>15 mg/m ²)
Etoposide	Procarbazine (oral)
Fluorouracil (<1000 mg/m ²)	<i>Level 5 (More Than a 90% Frequency)</i>
Gemcitabine	Carmustine (>250 mg/m ²)
Methotrexate (>50 mg/m ² ; <250 mg/m ²)	Cisplatin (≥50 mg/m ²)
Mitomycin	Cyclophosphamide (>1500 mg/m ²)
Paclitaxel	Dacarbazine (≥500 mg/m ²)
Teniposide	Lomustine (>60 mg/m ²)
Thiotepa	Mechlorethamine
Topotecan	Pentostatin
	Streptozocin

^aThe most highly emetogenic agent in the combination should be identified, and the contribution of other agents should be considered by using the following rules: (1) Level 1 agents do not contribute to the emetogenicity of a given regimen. (2) Adding one or more level 2 agents increases the emetogenicity of the combination by one level greater than the most emetogenic agent in the combination. (3) Adding level 3 and 4 agents increases the emetogenicity of the combination by one level per agent.

^bWhen methotrexate and cytarabine are coadministered intrathecally to pediatric patients, the level of emetogenicity is increased to level 3.

^cCorticosteroids should not be used as antiemetics.

Table 4.
Risk Factors for Chemotherapy-Induced Emesis^a

<i>Treatment-Specific Factors</i>	
Drug	
Dose	
Infusion rate	
<i>Patient-Specific Factors</i>	
Age	
Sex	
Alcohol use	
History of motion sickness or nausea during pregnancy	
Prior exposure to chemotherapeutic agents	

^aSee text for details.

diminishes, leaving the patient almost symptom-free by the end of the regimen. Emesis occurs earlier and is more severe when cytarabine is administered rapidly than when it is infused more slowly.⁶⁴

When more than one cycle of chemotherapy is given, emesis tends to be progressively less well controlled; however, with procarbazine, dacarbazine, bleomycin, and the androgens, nausea diminishes over repeated cycles as patients become more tolerant of the adverse effects. The degree of tolerance varies depending on the frequency of cycles, the interval between cycles, and the characteristics of the chemotherapy.

Likewise, in patients receiving chemotherapy over multiple days, including bone marrow transplant preparative regimens or leukemia induction regimens, emesis control declines after the first day and reaches a low by the third or fourth day. Emesis begins to resolve as the drugs are metabolized and excreted from the body. Patients receiving chemotherapy over multiple days experience both acute and delayed effects of the chemotherapeutic agents employed.^{16,67} Strategies for preventing emesis over multiple-day cycles usually employ antiemetics aimed at preventing symptoms of acute emesis on the first day and symptoms of both acute and delayed emesis for up to six days after the period of acute emesis.

The administration of drugs at specific times during the circadian or biological cycle also may affect the frequency and severity of chemotherapy-induced emesis. Patients receiving cisplatin during the evening hours (at or after 1800) have less emesis than those who receive the same dose in the morning (at or after 0600).⁶⁸

Other factors may also contribute to the overall risk of nausea and vomiting (Table 1) but not necessarily increase the frequency or severity of nausea and vomiting secondary to chemotherapy.

Prevention of Chemotherapy-Induced Nausea and Vomiting

Recommendation 1. The emetic potential of the chemotherapeutic agent (Table 3) is the primary factor to consider when deciding whether to administer pharmacologic prophylaxis and which antiemetic(s) to select. (Strength of evidence = A)

Table 3 shows a method for determining the emetic potential of combination therapy. The method has been adapted from an article published by Hesketh and colleagues.⁵⁷ In contrast to previously developed algorithms, this method includes newer chemotherapeutic agents and takes into account factors such as dose, route, and combination chemotherapy. The table was created on the basis of panel consensus after examination of clinical trials that used

Table 5.
Onset and Duration of Emesis^{16,63-66}

Chemotherapeutic Agent	Onset of Emesis after Administration (hr)	Duration of Emesis (hr)
Aldesleukin	0-6	N.A. ^a
Androgens	48-100 ^b	Variable
Asparaginase or pegaspargase	1-3	N.A.
Bleomycin	3-6	N.A.
Busulfan	N.A.	N.A.
Carboplatin (200-400 mg/m ²)	2-6	1-48
Carmustine	2-6	4-24
Chlorambucil (oral)	48-72	N.A.
Cisplatin	1-6	>24
Cladribine	N.A.	N.A.
Corticosteroids	N.A.	N.A.
Cyclophosphamide ^c	6-12	6-36
Cytarabine (>1000 mg/m ²)	6-12	3-5
Dacarbazine ^d	2-6	6-24
Dactinomycin	2-6	12-24
Daunorubicin	2-6	<24
Docetaxel	N.A.	N.A.
Doxorubicin	2-6	6-24
Etoposide	3-6	6-12
Fludarabine	N.A.	N.A.
Fluorouracil	3-6	3-6
Gemcitabine	N.A.	N.A.
Hydroxyurea	6-12	N.A.
Idarubicin	N.A.	N.A.
Ifosfamide	3-6	6-12
Interferon-beta	N.A.	N.A.
Irinotecan	2-6	6-12
Lomustine	3-6	6-12
Mechlorethamine	0.5-2	6-24
Melphalan (oral)	6-12	N.A.
Mercaptopurine	4-8	N.A.
Methotrexate	4-12	3-12
Mitomycin	2-6	18-24
Mitoxantrone (<15 mg/m ²)	N.A.	N.A.
Paclitaxel	N.A.	N.A.
Pentostatin	N.A.	N.A.
Procarbazine (oral) ^b	24-27	Variable
Semustine	3-6	6-12
Streptozocin	2-6	12-24
Teniposide	3-6	6-12
Thioguanine	4-8	N.A.
Thiotepa	6-12	Variable
Vinblastine	4-8	N.A.
Vincristine	4-8	N.A.

^aNot available.

^bDevelopment of tolerance possible.

^cHigh dose.

^dCharacteristically, vomiting lessens with each subsequent dose when dacarbazine is given over five days.

chemotherapeutic agents, antiemetic review articles that addressed emetogenic classification, and antiemetic trials that contained a placebo control as well as the collective clinical experience of the panel. The recommendations for combined therapy need to be validated in several patient populations. The table provides the framework for recommendations on whether to provide antiemetic prophylaxis for patients and on the selection of agents. Newer agents that are not included in the guidelines established by Hesketh et al. have been added to the table on the basis of the literature and panel consensus. This table was developed for adult patients and should be used cautiously in the pediatric population because of different degrees of emetogenicity, different dosages, and different combinations of chemo-

therapeutic agents used in this patient group. However, the table is considered to be generally applicable to children receiving chemotherapeutic agents.

Recommendation 2. Adult and pediatric patients receiving chemotherapeutic agent(s) with emetic potential classified as level 2 through 5 should receive pharmacologic prophylaxis against nausea and vomiting each day on which chemotherapy is given. (Strength of evidence = B) Antiemetic prophylaxis is not required when the level of emetogenicity is 1.

(a) Adult and pediatric patients receiving level-2 chemotherapeutic regimens can receive dexamethasone or methylprednisolone alone for prophylaxis of nausea and vomiting. (Strength of evidence = B) Prochlorperazine is also an option for adults. (Strength of evidence = D)

(b) Adult and pediatric patients receiving chemotherapeutic agent(s) with emetic potential of level 3 through 5 should receive a corticosteroid (dexamethasone or methylprednisolone) in combination with a 5-HT₃ receptor antagonist. (Strength of evidence = A for adults and C for pediatric patients)

(c) Orally and intravenously administered antiemetics are generally equivalent in efficacy and safety for both adult and pediatric patients. (Strength of evidence = B for adults and C for pediatric patients) The decision as to which formulation to use should be based on patient-specific factors and cost.

(d) The decision as to which 5-HT₃ receptor antagonist to use should be based on the acquisition cost of comparable doses. (Strength of evidence = A) (Tables 6 and 7) Dosage recommendations for adult and pediatric patients differ.

Efficacy of 5-HT₃ Receptor Antagonists. Ondansetron, granisetron, and dolasetron prevent the serotonin-stimulated emetic response by blocking the 5-HT₃ receptors of the vagal afferent nerves in the GI tract and the CTZ. Clinical trials have demonstrated the safety and efficacy of ondansetron, granisetron, and dolasetron for the prevention of acute nausea and vomiting in pediatric and adult patients, including patients receiving moderately emetogenic (cyclophosphamide) or highly emetogenic (cisplatin) chemotherapeutic agents.^{41,42,46,47,69-108}

The safety of granisetron, ondansetron, and dolasetron has been demonstrated in clinical trials, with headache being the most common event (14%) and asthenia (5%), somnolence (4%), diarrhea (4%), constipation (3%), and fever (<1%) occurring infrequently. These effects are not dose or route dependent. A safety advantage of the 5-HT₃ receptor antagonists over metoclopramide has been demonstrated. In one study, the frequency of adverse effects was significantly less with granisetron than with metoclopramide (61% versus 77% respectively, $p = 0.003$).¹⁰⁹ Extrapyramidal effects and agitation were significantly less frequent ($p < 0.0001$ and $p = 0.030$, respectively) with ondansetron than with metoclopramide.

In general, the 5-HT₃ receptor antagonists are well-tolerated agents. Few patients have withdrawn from clinical trials of these agents because of adverse effects. Significant differences among the 5-HT₃ receptor antagonists in the rate of adverse effects have generally not been seen.

The 5-HT₃ receptor antagonists as a class may cause electrocardiographic (ECG) interval changes (PR, Q_{Tc}, and ST prolongation and QRS widening). With dolasetron, these changes are related in magnitude and frequency to blood

levels of the active metabolite hydrodolasetron. These ECG changes are thought to occur secondary to the blockade of sodium channels.¹¹⁰ The effects of dolasetron versus ondansetron on ECG recordings were studied in healthy volunteers.¹¹¹ The changes were acute, transient, and asymptomatic. Dolasetron was associated with significant dose-related increases in heart rate and PR and QRS intervals between zero and four hours. Ondansetron produced a significant increase in QT interval and decrease in heart rate. All values returned to baseline after eight hours.

5-HT₃ Receptor Antagonists versus Metoclopramide.

Ondansetron, granisetron, and dolasetron have been compared with metoclopramide, with and without dexamethasone, in cisplatin-treated adult patients.^{44,79,83,91,112-120} A large double-blind, randomized study examined the efficacy and safety of antiemetic prophylaxis with either ondansetron (0.15 mg/kg i.v. for three doses starting 30 minutes before chemotherapy and then every two hours for two doses) plus dexamethasone phosphate (20 mg i.v. daily) or metoclopramide (3 mg/kg i.v. given 30 minutes before chemotherapy and two hours after chemotherapy) plus dexamethasone phosphate (20 mg i.v. daily) and diphenhydramine hydrochloride (50 mg i.v. daily) in patients receiving cisplatin at a dose of at least 50 mg/m².¹²¹ Complete protection from vomiting was found more frequently in the patients receiving ondansetron plus dexamethasone (79%) than in the patients receiving the metoclopramide combination (60%, $p < 0.002$).¹²² These results were maintained for up to three consecutive cycles of chemotherapy.

Similar results have been found in patients receiving granisetron or dolasetron. In a double-blind, randomized study comparing granisetron (1 mg orally twice daily) alone, granisetron (1 mg orally twice daily) plus dexamethasone phosphate (12 mg i.v. on day 1 only), and metoclopramide (3 mg/kg as a loading dose before cisplatin with a 4-mg/kg i.v. infusion over eight hours administered at the same time as cisplatin, and, on days 1–6, metoclopramide 10 mg orally three times daily) plus dexamethasone phosphate (12 mg i.v. on day 1) in patients receiving cisplatin at a dose of at least 50 mg/m², complete protection from emesis and nausea was found in 43.7%, 54.7%, and 37.2%, respectively, on the day cisplatin was administered.¹¹⁵ The granisetron–dexamethasone combination was superior to both granisetron alone and the metoclopramide–dexamethasone combination ($p = 0.007$).

In a multicenter, double-blind, randomized trial, the efficacy and safety of dolasetron 1.2 or 1.8 mg/kg i.v. and metoclopramide 7 mg/kg i.v. were compared in 226 patients for the prevention of acute nausea and vomiting associated with high-dose cisplatin (>80 mg/m²).¹¹⁹ Complete response was obtained in 57% of patients receiving dolasetron 1.8 mg/kg, 48% of patients receiving dolasetron 1.2 mg/kg, and 35% of patients receiving metoclopramide. Both doses of dolasetron were more effective ($p = 0.0009$ for 1.8 mg/kg, $p = 0.0058$ for 1.2 mg/kg) than metoclopramide. Twelve percent of the patients receiving metoclopramide reported extrapyramidal symptoms, which is not unexpected with the large doses that were used.¹¹⁹

Studies have shown that, in patients receiving moderately emetogenic chemotherapy, ondansetron (8 mg orally three times daily, with the first dose sometimes administered intravenously) is at least as effective as metoclopramide (60 mg i.v. followed by 20 mg orally three times daily) and better tolerated.¹²³⁻¹²⁵

Table 6.
Standard Dosages and Costs of Antiemetics for Management of Chemotherapy-Induced Nausea and Vomiting in Adults

Agent	Dosage	Cost/Dose (\$) ^a	Cost/Day(\$) ^a
<i>Prophylaxis</i>			
Ondansetron ^b	24 mg p.o. (tablet or suspension) 30 min before chemotherapy	38.46	... ^c
Granisetron ^b	8 mg i.v. 30 min before chemotherapy	48.90	...
	2 mg p.o. 30 min before chemotherapy	82.56	...
	10 µg/kg i.v. 30 min before chemotherapy	121.77 ^d	...
Dolasetron ^b	100–200 mg p.o. 30 min before chemotherapy	66.00	...
	1.8 mg/kg or 100 mg i.v. 30 min before chemotherapy	149.88	...
Dexamethasone ^f	20 mg p.o. 30 min before chemotherapy	1.60	...
	20 mg i.v. 30 min before chemotherapy	3.08	...
<i>Treatment</i>			
Lorazepam	1–2 mg p.o. or sl q 6 hr	0.19–0.38	0.76–1.52
	1–2 mg i.m. or i.v. q 6 hr	5.19–10.30	20.76–41.52
Prochlorperazine	5–20 mg p.o. q 6 hr	2.54–2.16	2.16–8.64
	5–20 mg i.m. or i.v. q 6 hr	1.10–4.38	4.40–17.52
	25 mg rectally q 12 hr	3.39	6.78
	15–30 mg (extended-release capsule) p.o. q 12 hr	1.64–3.28	3.28–6.00
Metoclopramide	2 mg/kg i.v. q 2–4 hr for 2–5 doses; for delayed nausea and vomiting, 0.5 mg/kg or 30 mg i.v. q 4–6 hr for 3–5 days	3.94	7.88–19.70
	2 mg/kg p.o. q 2–4 hr for 2–5 doses; for delayed nausea and vomiting, 0.5 mg/kg or 30 mg p.o. q 4–6 hr for 3–5 days	0.51	1.02–2.55
Dexamethasone	10–20 mg p.o. q 4–6 hr	0.80–1.60	3.20–9.60
	10–20 mg i.v. q 4–6 hr	2.33–4.22	9.32–27.96
Haloperidol	1–4 mg p.o. q 6 hr	0.20–0.80	0.80–3.12
	1–4 mg i.m. or i.v. q 6 hr	0.75–3.00	3.00–12.00
Dronabinol	5–15 mg/m ² (~5–20 mg) p.o. q 3–6 hr	5.87–22.49	23.48–179.92

^a1998 Red Book.

^bFor use with chemotherapeutic agents having an emetogenic potential of level 3, 4, or 5.

^cNot applicable.

^dFor a 70-kg patient.

^eFor use with chemotherapeutic agents having an emetogenic potential of level 2, 3, 4, or 5. Not recommended for use with aldesleukin.

Selecting a 5-HT₃ Receptor Antagonist. At equipotent doses, granisetron, ondansetron, and dolasetron do not appear to differ in efficacy or safety in patients treated with moderately or highly emetogenic chemotherapeutic regimens.^{90,91,105,107,126-139} The comparative trials included a variety of combinations of chemotherapeutic agents as well as i.v. and oral antiemetic therapies at varying regimens. Two of the most recent trials were performed by Navari et al.¹⁰⁵ and Roila.¹³⁶ The study by Navari et al. was a large, double-blind study in which ondansetron (0.15 mg/kg i.v. for three doses) was compared with granisetron (10 or 40 mg/kg i.v.) in 987 chemotherapy-naïve patients receiving cisplatin (>70 mg/m²). The rate of complete protection from vomiting was similar among all three groups (51%, 47%, and 48%, respectively; $p > 0.05$). Neither agent was used in combination with dexamethasone.

In the study by Roila,¹³⁶ ondansetron 8 mg plus dexamethasone phosphate 20 mg i.v. was compared with granisetron 3 mg and dexamethasone phosphate 20 mg i.v. in 973 chemotherapy-naïve patients receiving cisplatin at a dose of at least 50 mg/m². Neither group received the doses approved by FDA for the prevention of emesis in patients receiving highly emetogenic chemotherapy. The doses used were those approved by regulatory agencies in Europe (where the study was performed) for this indication. Complete protection from vomiting was similar between the two groups (79.3% and 79.9%, respectively).

A randomized, double-blind, parallel trial compared dolasetron 1.8 or 2.4 mg/kg i.v. with ondansetron 32 mg i.v. for the prevention of nausea and vomiting after highly

emetogenic chemotherapy.¹³⁸ All treatments were given over 15 minutes beginning 30 minutes before cisplatin administration. The complete response rates for dolasetron 1.8 and 2.4 mg/kg and ondansetron were 44.4%, 40%, and 42.7%, respectively. No significant differences were noted among treatment groups.

Granisetron and ondansetron were shown in a multicenter trial not to differ significantly in their effect on functional status (as defined by using the FLIE) before and 72 hours after cancer chemotherapy.¹⁴⁰

The results of these trials and other data suggest that the choice of whether to use ondansetron, dolasetron, or granisetron should be based primarily on acquisition costs for comparable dosage regimens.

Intravenous versus Oral 5-HT₃ Receptor Antagonists. If adult or pediatric patients are able to take medication orally, therapy should generally be given via that route. There is strong evidence to support the use of oral dolasetron and granisetron in adult patients receiving highly emetogenic chemotherapy. There are as yet few published data to support the use of oral ondansetron in adult patients receiving highly emetogenic chemotherapy or the use of oral 5-HT₃ receptor antagonists in pediatric patients receiving highly emetogenic chemotherapy. Oral administration may obviate the need for i.v. access, is easier in outpatients, is usually less expensive, and is generally preferred over the i.v. route by the patient if he or she does not have i.v. access. Preclinical studies also suggest that oral therapy may have an advantage

Table 7.
Standard Dosages and Costs of Antiemetics for Management of Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients

Drug	Dosage	Cost(\$) ^a		
		Per Regimen	Per Dose	Per Day
<i>Prophylaxis</i>				
Ondansetron	If 4–11 yr of age, 4 mg p.o. 30 min before and 4 and 8 hr after chemotherapy; may also be given as a single 12-mg dose 30 min before chemotherapy	34.65		
	If >11 yr of age, 8 mg p.o. 30 min before and 4 and 8 hr after chemotherapy; may also be given as single 24-mg dose 30 min before chemotherapy	55.02		
	If >3 yr of age, 0.15 mg/kg i.v. 30 min before and 4 and 8 hr after chemotherapy	146.70		
Granisetron	If ≥2 yr of age, 20–40 µg/kg i.v. 30 min before chemotherapy	34.79–69.58		
Dexamethasone	10–14 mg/m ² p.o. in single or divided doses	1.44		
	10–14 mg/m ² i.v. in single or divided doses	4.41		
Dolasetron	1.8 mg/kg p.o. 30 min before chemotherapy	49.80		
	1.8 mg/kg i.v. 30 min before chemotherapy	53.95		
Methylprednisolone	0.5–1 mg/kg p.o. 30 min before and 4 and 8 hr after chemotherapy (maximum total dose, 4 mg/kg); may also be given as single dose 30 min before chemotherapy	4.05–8.10		
	0.5–1 mg/kg i.v. 30 min before and 4 and 8 hr after chemotherapy (maximum total dose, 4 mg/kg); may also be given as single dose 30 min before chemotherapy	1.80–3.60		
<i>Treatment</i>				
Lorazepam	0.05 mg/kg (maximum, 3 mg) p.o. q 8–12 hr as needed		0.19	0.57–1.14
	0.05 mg/kg (maximum, 3 mg) i.v. q 8–12 hr as needed		5.19	15.57–31.14
Chlorpromazine	If >6 mo of age, 0.55 mg/kg p.o. q 4–6 hr as needed		0.07	0.28–0.42
	If >6 mo of age, 1.1 mg/kg rectally q 6–8 hr as needed (maximum of 40 mg per dose if age is <5 yr or weight is <22 kg)		3.25	9.75–13.00
	If >6 mo of age, 0.55 mg/kg i.v. q 6–8 hr as needed (maximum of 40 mg per dose if age is <5 yr or weight is <22 kg)		0.26	0.78–1.04
Methylprednisolone	0.5–1 mg/kg p.o. q 12 hr as needed		1.62–2.70	3.24–5.40
	0.5–1 mg/kg i.v. q 12 hr as needed		0.60–1.20	1.20–2.40
Dexamethasone	5–10 mg/m ² p.o. q 12 hr as needed		0.48–1.44	0.96–2.88
	5–10 mg/m ² i.v. q 12 hr as needed		1.19–2.33	2.34–4.66

^aBased on 1998 *Red Book* prices. For 20-kg child or child with body surface area of 0.8 m².

over i.v. therapy because the oral formulation may act locally on the GI serotonin receptors.^{36,141} There will be situations in which the i.v. route is preferred (e.g., patients unable to take oral medication because of vomiting at the time of or shortly after administration; pediatric patients receiving multidrug, highly emetogenic drug combinations).

The efficacy and safety of an oral antiemetic regimen versus i.v. therapy was examined in patients receiving moderately and highly emetogenic chemotherapy in three recent studies.^{135,142,143} In the trials by Perez et al.¹³⁵ and Gralla et al.,¹⁴² 2 mg of oral granisetron was comparable in efficacy to 32 mg of i.v. ondansetron, with no significant difference in adverse events. In a study by Navari et al.,¹⁴³ the oral combination of dolasetron and dexamethasone was associated with a clinically relevant longer time to first emetic episode than i.v. dolasetron and dexamethasone. Although there are some data showing that oral ondansetron may not be equivalent to the i.v. formulation, inadequate doses may have been used.¹¹⁷

Selecting a Dose of 5-HT₃ Receptor Antagonist. Several dose-finding studies have shown that ondansetron administered as a single i.v. dose of 8 or 32 mg is as effective as the formerly recommended multiple-dose regimen (0.15 mg/kg plus two additional doses administered at least four hours apart) or an infusion regimen (8 mg plus a continuous infusion of 1 mg/hr for 24 hours) in patients receiving high doses of cisplatin.^{73,144,145} Seynaeve et al.¹⁴⁴ evaluated 535 patients who received a single 32-mg i.v. dose of ondansetron, an 8-mg i.v. dose followed by a continuous infusion of 1 mg/hr for 24 hours, or a single 8-mg i.v. dose given before cisplatin chemotherapy. Control of emesis was similar among the three groups. Other studies support the efficacy of using an 8-mg dose.^{127,146}

In a study by Hesketh and colleagues,⁶⁵ the efficacy and safety of i.v. ondansetron 32, 24, and 8 mg each combined with 20 mg of i.v. dexamethasone phosphate were examined in patients receiving chemotherapy of high, moderately high, or moderate emetic potential, respectively. This

was not a randomized trial but a trial in which the different doses were based on chemotherapy treatments the patients received. Patients had good control of acute emesis across a wide spectrum of chemotherapy regimens, with a complete response obtained in 72%, 88%, and 77% of patients in the high, moderately high, and moderate categories, respectively. Roila et al.¹³⁶ demonstrated the equivalence of ondansetron 8 mg i.v. with granisetron 3 mg i.v. when each was used with i.v. dexamethasone. In a large-scale, double-blind study involving 699 patients, the efficacy of ondansetron 32 mg i.v. was found to be superior to the 8-mg i.v. dose.¹⁴⁵

On the basis of these studies, a single dose of 8 mg i.v. is recommended for most adult patients if ondansetron is used for the prevention of nausea and vomiting in patients receiving chemotherapy of emetogenic levels 3 to 5. Most of the data supporting i.v. ondansetron doses of 8 mg were based on cisplatin regimens administered in doses of 75 mg/m², on average. It is unclear whether patients receiving cisplatin doses exceeding 100 mg/m² would benefit from higher ondansetron doses. In pediatric patients, 0.15 mg/kg has been used, but lower doses may be effective. Tables 6 and 7 list the recommended dosages for adult and pediatric patients.

The efficacy and tolerability of ondansetron 24 mg orally plus dexamethasone 12 mg orally were compared with the efficacy and tolerability of ondansetron 8 mg i.v. plus dexamethasone phosphate 20 mg i.v. in patients receiving highly emetogenic chemotherapy.¹⁴⁷ A total of 562 patients were randomly assigned to receive oral (262 patients) or i.v. (266 patients) therapy. Complete or major control of emesis was achieved in 90% of the patients in the oral group and 89% in the i.v. group. There was no significant difference in efficacy or tolerability between 24 mg of oral ondansetron plus dexamethasone and 8 mg of i.v. ondansetron plus dexamethasone in the prevention of acute nausea and vomiting with highly emetogenic chemotherapy.

Many of the available studies with i.v. granisetron have used 40 mg/kg instead of the 10-mg/kg dose approved by FDA. However, clinical studies have shown that both doses are comparable in most patients, and therefore it is recommended that 10 mg/kg or 1 mg be used in adults.^{97,148,149} This was further confirmed in a recent large-scale clinical trial in which a 1-mg i.v. dose was similar in efficacy to a 3-mg i.v. dose.¹⁰⁵ In pediatric patients, doses higher than 10 mg/kg may be necessary.⁸⁰

Dose-ranging studies have been performed to determine the optimal dose of dolasetron for the prevention of nausea and vomiting^{102,104,150-158} in adult and pediatric patients.^{105,107,153-161} An i.v. dose of 1.8 mg/kg has been shown to be safe and effective in adults and pediatric patients. Oral doses of 25, 50, 100, and 200 mg in adults were compared in a pooled analysis performed by Rubenstein et al.¹⁵⁴ in patients receiving moderately emetogenic chemotherapy. Fewer patients who received the 25-mg dose had a complete response compared with those who received the 100- and 200-mg dose ($p < 0.001$). The difference between the 100- and 200-mg dose was not significant ($p = 0.052$); therefore, the 100-mg oral dose is recommended for the prevention of nausea and vomiting in adult patients receiving moderately emetogenic chemotherapy, but a dose of 200 mg may be required in patients receiving highly emetogenic chemotherapy.

Combining 5-HT₃ Receptor Antagonists with Dexamethasone. When combination antiemetic therapy is being considered, agents with different mechanisms of action should

be selected if possible. The mechanism by which corticosteroids exert their antiemetic activity is unknown, but investigators have theorized that it may be inhibition of prostaglandin synthesis or modification of the blood-cerebrospinal fluid barrier for chemotherapeutic agents. Another theory is that corticosteroids inhibit cortical input into the vomiting center. Several double-blind, large-scale trials have shown that the combination of ondansetron or granisetron with dexamethasone is significantly more effective than either agent alone against high-dose cisplatin-induced emesis.^{67,68,98,115,139,159-168}

In a study by Joss,¹⁶⁹ 215 patients were randomly assigned to receive ondansetron 8 mg i.v. plus placebo or the same dose of ondansetron with dexamethasone phosphate 8 mg i.v. 15 minutes before and four and eight hours after administration of highly emetogenic chemotherapy. In chemotherapy-naïve patients, the combination of ondansetron plus dexamethasone was significantly better than ondansetron and placebo in protecting the patients completely from emesis (81% versus 64%, respectively; $p = 0.04$).

The combination of granisetron with dexamethasone has been found to be superior to granisetron alone in patients receiving moderately emetogenic chemotherapeutic agents. One study evaluated 428 patients who were being treated with moderately emetogenic chemotherapy (cyclophosphamide 600–1000 mg/m², doxorubicin >50 mg/m², epirubicin >75 mg/m², or carboplatin >300 mg/m² alone or in combination) and randomly assigned to receive one of three antiemetic drug regimens.¹⁶² One group of patients received dexamethasone phosphate 8 mg i.v. before chemotherapy and dexamethasone 4 mg orally immediately before the start of chemotherapy and every 6 hours for 24 hours (four doses). Another group received granisetron 3 mg i.v. 20 minutes before chemotherapy. A third group received the combination of granisetron and dexamethasone (granisetron 3 mg i.v. 20 minutes before chemotherapy, followed by dexamethasone phosphate 8 mg i.v., then dexamethasone 4 mg orally immediately before the start of chemotherapy; the dexamethasone dose was repeated every six hours for a total of four doses). Patients who received the combination regimen were found to have complete protection from vomiting, nausea, and both nausea and vomiting (93%, 72%, and 70%, respectively) more frequently compared with those who received dexamethasone (71%, 55%, and 49%) and granisetron alone (72%, 48%, and 43%). Combination therapy was significantly better than either agent alone in providing complete protection from either nausea or vomiting. This effect was maintained through several cycles of chemotherapy.¹⁶³ Dexamethasone alone was as effective as granisetron alone in preventing emesis induced by moderately emetogenic chemotherapy.

Similar to ondansetron and granisetron, the efficacy of dolasetron was enhanced by the addition of dexamethasone.¹³⁹

Although there has been concern that corticosteroids may interfere with the antitumor effects of chemotherapy through immunosuppressive mechanisms, this has not been documented in clinical trials. The known benefits of corticosteroids as antiemetics outweigh these unproven theoretical concerns. However, this may not be the case with some biological agents, such as aldesleukin. The coadministration of glucocorticoids such as dexamethasone with aldesleukin should be avoided.¹⁷⁰ Interleukin-2 produced by T-helper cells stimulates the production of the immune system's T-killer cells to activate an immune response against the

tumor. Dexamethasone may decrease the antitumor effectiveness of aldesleukin by inhibiting the activity of the T-helper cells, thereby decreasing T-killer-cell activity.¹⁷¹⁻¹⁷³

Corticosteroids are used for the treatment of many malignancies and are usually administered as a single dose before chemotherapy. It is extremely unlikely that using these agents as antiemetics in this way would lead to clinically significant adverse reactions. Corticosteroids should be used with caution in patients with unstable diabetes mellitus. Data supporting the use of additional agents (e.g., D₂ antagonists) in combination with 5-HT₃ receptor antagonists are emerging.¹⁷⁴

Use of Dexamethasone Alone or Prochlorperazine with Mildly to Moderately Emetogenic Chemotherapy. High doses of corticosteroids, such as methylprednisolone 250 mg and dexamethasone 20 mg, given intravenously or orally, have demonstrated useful antiemetic activity when used alone for the prevention of acute nausea in patients receiving mildly to moderately emetogenic chemotherapy.¹⁷⁵⁻¹⁷⁹ Dexamethasone has been shown to be at least as effective as prochlorperazine in these patients.^{178,179} Markman et al.¹⁷⁸ demonstrated that patients receiving moderately emetogenic chemotherapy have significantly less nausea and vomiting ($p < 0.02$ and $p < 0.03$, respectively), less somnolence ($p < 0.001$), and less suppression of appetite ($p < 0.02$) with dexamethasone than with prochlorperazine. Few associated effects are reported with dexamethasone and include mood changes, increased appetite, and a feeling of well-being.

Prochlorperazine is a reasonable alternative to dexamethasone in adults. Phenothiazines, such as prochlorperazine, were the first agents reported to provide significant antiemetic activity in patients receiving chemotherapy and have been used for more than 30 years.^{179,180} They have been shown to be effective in the prevention of nausea and vomiting in patients receiving mildly to moderately emetogenic chemotherapy.

Pediatrics. Several reports support the safety and efficacy of ondansetron, granisetron, and dolasetron in pediatric patients.^{75,80,89,92,96,100-104,106,171,181-184} Ondansetron is commercially available as an oral solution, whereas granisetron and dolasetron are not. Granisetron hydrochloride injection has been shown to be stable in apple juice, orange juice, cola, and electrolyte-replacement solution for at least one hour when stored at room temperature.^{185,186} Dolasetron injection mixed in apple or apple-grape juice may be kept for up to two hours at room temperature before use.¹¹⁰

Ondansetron was compared with metoclopramide plus dexamethasone in a randomized, controlled study of 30 patients ages 1 to 15 years who received moderately emetogenic chemotherapeutic agents.¹⁰¹ Patients received ondansetron 3–8 mg/m² i.v. over three to five minutes before chemotherapy followed by 3–8 mg/m² i.v. or orally and every 12 hours for three days. Intravenous metoclopramide was given at a dose of 10 mg/m² before chemotherapy and every six hours for at least three days. Dexamethasone was given at a dose of 2 or 4 mg/m² i.v. or orally three times daily. In the 24 hours after the start of chemotherapy, ondansetron was more effective than the metoclopramide–dexamethasone combination: 93% of patients receiving ondansetron and 33% of patients receiving metoclopramide in combination with dexamethasone had a complete (no emetic episodes) or major (1 to 2 emetic episodes) response. The dose of metoclopramide in this study (approximately 0.33 mg/kg) was low. Most studies that have demonstrated the efficacy of

metoclopramide for chemotherapy-induced nausea and vomiting have used doses greater than 1 mg/kg.

Similar results were found by Hahlen and colleagues¹⁰² when granisetron was compared with a chlorpromazine–dexamethasone combination. Children were assigned on a single-blind basis to receive either granisetron or a combination of dexamethasone and chlorpromazine for the duration of ifosfamide treatment (two to three days). On each treatment day, granisetron 20 mg/kg was infused immediately before ifosfamide. Two subsequent doses (20 mg/kg) were permitted within each 24-hour period. In the other group, dexamethasone phosphate 2 mg/m² was infused 30 minutes before ifosfamide therapy each day, followed by 2 mg/m² 8 and 16 hours later. At the start of the study, the chlorpromazine dosage was 0.5 mg/kg i.v. 25 minutes before ifosfamide infusion and at four- to six-hour intervals. This dosage proved too sedating and was subsequently reduced to 0.3 mg/kg followed by 0.3–0.5 mg/kg at four- to six-hour intervals. During the first 24 hours, 50% of the patients in the granisetron group experienced either no vomiting or one vomiting episode, compared with 21% of the patients in the chlorpromazine and dexamethasone group ($p = 0.005$).

Dolasetron has been used in the pediatric population.^{104,106} Doses of 0.6–2.4 mg/kg were evaluated in 46 children receiving moderately to highly emetogenic chemotherapy.¹⁰⁴ Complete response rates ranged from 10% to 67% and did not necessarily correlate with dose.

The value of adding dexamethasone to a 5-HT₃ receptor antagonist was evaluated in a study by Alvarez et al.⁹⁸ involving 34 children 3 to 18 years of age. The children were given ondansetron 0.15 mg/kg i.v. 30 minutes before chemotherapy and at four and eight hours in combination with either placebo or dexamethasone 4–8 mg/m² i.v. every four to six hours. All the patients received highly emetogenic chemotherapy, including cisplatin, cyclophosphamide, and ifosfamide. Complete response (no episodes of emesis) occurred in 61% of the patients who received ondansetron plus dexamethasone and 23% of the patients who received ondansetron plus placebo. Significance was not determined. Although a total dose of 0.45 mg/kg was used, reduced doses of ondansetron have been shown to be effective.

Both dexamethasone and methylprednisolone are used in pediatric patients. Although most of the literature supporting the addition of corticosteroids relates to dexamethasone, the risk of perineal irritation is lower with methylprednisolone.¹⁸⁷ In adult patients, this adverse effect has been shown to be minimized by slowing the infusion rate. Although corticosteroids can be used, many children receiving moderately emetogenic chemotherapy regimens have leukemia or lymphoma and already receive a corticosteroid as part of their chemotherapy regimen.

Chlorpromazine has been shown to be effective in pediatric patients receiving moderately emetogenic chemotherapeutic agents.¹⁸⁸⁻¹⁹² One of the most frequent adverse effects of chlorpromazine is sedation.

Pharmacoeconomic Issues. Johnson and colleagues¹⁹³ evaluated the clinical and economic outcomes associated with the use of ondansetron in patients receiving chemotherapy. The objectives of the study were to (1) retrospectively compare lengths of hospital stay and overall hospital costs for patients receiving ondansetron or “standard” antiemetic therapy, (2) concurrently examine the hospital costs associated with managing an episode of severe nausea and vomiting in patients receiving chemotherapy, and (3) concurrently com-

pare quality-of-life scores for patients admitted for chemotherapy who received ondansetron or standard therapy. The recommended indication for ondansetron at the study institution was for patients receiving moderately to highly emetogenic chemotherapy or patients intolerant to other antiemetic regimens. Ondansetron was not used routinely to prevent or treat delayed episodes of nausea and vomiting. The standard dosage regimen for ondansetron at the study institution was the manufacturer's recommended dose of 0.15 mg/kg i.v. over 15 minutes, 30 minutes before chemotherapy, and four and eight hours later for each cycle of chemotherapy. The study by Johnson et al. supports a shorter hospital stay for patients who received ondansetron than for those who received standard therapy when severity of illness and disease are controlled for. The hospital costs per admission were lower, hospital revenue per admission was higher, and resource consumption was lower in the patients receiving ondansetron versus the standard therapy group. Of the 52 patients who were asked to participate in the quality-of-life analysis, 27 completed the FLIC portion of the questionnaire. Mean scores were lower after chemotherapy was administered in both the ondansetron and standard therapy groups; there was not a significant difference between the two groups. Major limitations of this study were that standard antiemetic therapy and antineoplastic doses were not defined. Other studies that have examined the economic impact of 5-HT₃ receptor antagonists^{192,194-199} generally support their use with highly emetogenic chemotherapy. These studies differ in their methods and definitions of outcomes.

For the prevention of acute emesis, the 5-HT₃ receptor antagonists are more expensive than other antiemetics, but they are more effective. In an economic analysis conducted by Dranitsaris and colleagues,²⁰⁰ patients with breast cancer who received FEC or FAC chemotherapy (fluorouracil-epirubicin-cyclophosphamide or fluorouracil-doxorubicin-cyclophosphamide) and ondansetron for acute or delayed emesis were studied. Total costs (primary, rescue, and failure costs) were \$56.73 and \$51.31 for the ondansetron and comparator groups, respectively. Patients in the comparator group received metoclopramide i.v., diphenhydramine i.v., and lorazepam sublingually. Beyond the first 24 hours, 5-HT₃ receptor antagonists became an increasingly more expensive option (i.e., less value for money).

In contrast, Zbrozek and colleagues²⁰¹ suggested that ondansetron provides only a small benefit at a large overall cost compared with metoclopramide. There were, however, several limitations to their cost-utility analysis. The authors assumed that successful treatment of nausea and vomiting is analogous to the improvement of chronic mild to moderate angina. However, it is difficult to extrapolate the improvement in quality of life and satisfaction of patients with angina to cancer patients at high risk for chemotherapy-induced nausea and vomiting. In addition, the authors' definitions of successful treatment and associated costs were not inclusive or reflective of clinical practice. The time that patients were at risk for nausea and vomiting was arbitrarily set at one day. Because cost-utility analysis has an implied extrapolation to a full year (quality adjusted life year), this would make sense if chemotherapy were repeated every day. Because chemotherapy is usually repeated only once a month, the cost utility is reduced.

From pharmacoeconomic studies it appears that 5-HT₃ receptor antagonists are a cost-effective choice for adults and children receiving moderately to highly emetogenic agents.

Treatment of Breakthrough Chemotherapy-Induced Nausea and Vomiting

Recommendation 3. All patients receiving chemotherapy should have antiemetics available on an as-needed basis for rescue for breakthrough nausea and vomiting. (Strength of evidence = A) Patients should be educated on the appropriate administration of and expectations for therapy and should be reassured that every effort is being made to prevent symptoms. In adults, lorazepam, methylprednisolone, prochlorperazine, metoclopramide, dexamethasone, haloperidol, and dronabinol are effective. (Strength of evidence = C) In pediatric patients, chlorpromazine, lorazepam, or methylprednisolone (or dexamethasone) is recommended. (Strength of evidence = B) The choice of agent should be based on patient-specific factors (e.g., anticipated adverse effects, past success) and cost.

Agents available for the management of nausea and vomiting include chlorpromazine, prochlorperazine, methylprednisolone, lorazepam, metoclopramide, dexamethasone, haloperidol, and dronabinol. These agents differ in their mechanism of action, dosage, adverse effects, and cost.

Chlorpromazine, prochlorperazine, and haloperidol are thought to exert their antiemetic activity by inhibiting dopamine at the CTZ. The anticholinergic activity of these agents may also contribute to their antiemetic effects. Metoclopramide exerts its activity by inhibiting the dopamine receptors, and, at high doses, 5-HT₃ receptors in the GI tract and CTZ. Lorazepam is thought to inhibit the limbic system and cortical input into the vomiting center. The mechanism of action of dronabinol is unknown. The efficacy of these rescue medications, especially haloperidol, dronabinol, prochlorperazine, and promethazine, has not been well documented in the medical literature.

Tables 6 and 7 list recommended dosages and costs of lorazepam, chlorpromazine, prochlorperazine, metoclopramide, methylprednisolone, dexamethasone, haloperidol, and dronabinol for the treatment of chemotherapy-induced nausea and vomiting. At recommended dosages, these agents are generally associated with a low risk of adverse effects in most patients and are generally inexpensive. Metoclopramide has been associated with frequent adverse effects in children, including dystonic reactions.²⁰²⁻²⁰⁸ Table 2 lists the most common adverse effects of the different classes of agents used.

Granisetron, dolasetron, and ondansetron have also been shown to be effective in the treatment of breakthrough nausea and vomiting, but their superiority over more traditional, less expensive agents has not been determined. Results from several noncomparative trials demonstrate that ondansetron and granisetron are effective in treating chemotherapy-induced emesis refractory to conventional therapy.^{42,209-211}

The cannabinoids have complex central nervous system effects, including central sympathomimetic action. Evidence supports the selective use of pure tetrahydrocannabinol (THC) preparations to treat nausea associated with chemotherapy rather than the reclassification of crude marijuana as a prescribable medicine.²¹² Because the oral form of THC can be abused, only the amount necessary for a single cycle should be prescribed.

The reader is referred to recommendation 10 for guidance in managing patients who do not respond to initial therapy with an antiemetic agent.

Prevention of Delayed Chemotherapy-Induced Emesis

Recommendation 4. For the prevention of delayed emesis after cisplatin therapy in adults, dexamethasone with metoclopramide or a 5-HT₃ receptor antagonist is recommended. (Strength of evidence = A) The choice of agent should be based on patient-specific factors and cost. For delayed emesis after cyclophosphamide, doxorubicin, or carboplatin therapy, a 5-HT₃ receptor antagonist with dexamethasone is recommended. (Strength of evidence = B) Prochlorperazine in combination with dexamethasone has also been used and is available in extended-release and rectal dosage forms, but the evidence to support this combination is limited. (Strength of evidence = D) In pediatric patients, chlorpromazine, lorazepam, or a 5-HT₃ receptor antagonist can be used in combination with a corticosteroid. (Strength of evidence = C)

Delayed emesis occurs most frequently with cisplatin and cyclophosphamide. Patients who have problems with delayed nausea and vomiting during their initial cycle of chemotherapy are more likely to have an occurrence during subsequent cycles.

The use of metoclopramide in combination with dexamethasone was shown to be effective in a double-blind, controlled trial comparing placebo, dexamethasone, and the combination of dexamethasone and metoclopramide in cisplatin-treated patients.⁴⁸ Delayed vomiting was prevented in 11% of placebo recipients, 35% of patients receiving dexamethasone, and 52% of patients treated with the combination of metoclopramide and dexamethasone, with the greatest benefits at two to three days after cisplatin therapy. Patients received dexamethasone 8 mg orally twice daily for two days then 4 mg orally twice daily for two days plus metoclopramide 0.5 mg/kg orally four times daily for four days.

Oral ondansetron was shown to be effective in a randomized placebo-controlled trial.²¹³ The patients who received ondansetron had significantly fewer emetic episodes on days 2 and 3 combined, day 4, and day 5 than the patients who received placebo ($p < 0.002$). On days 2 and 3, the complete response rate was 36% for patients receiving ondansetron and 26% for placebo recipients.

The Italian Group for Antiemetic Research²¹⁴ compared the efficacy and safety of oral ondansetron 8 mg twice daily with that of oral metoclopramide 20 mg every six hours, both combined with intramuscular dexamethasone phosphate (8 mg twice daily on days two and three and 4 mg twice daily on day four), in 322 patients who had been given cisplatin 50 mg/m² or more. All patients received the same i.v. prophylactic regimen for acute emesis (ondansetron 8 mg and dexamethasone phosphate 20 mg). Complete protection from delayed emesis and nausea was achieved in 62% and 44% of patients with ondansetron and 60% and 54% of patients with metoclopramide, respectively. These differences were not significant ($p \geq 0.05$). There was no difference in the occurrence of adverse effects between the two groups, with the exception of constipation and heartburn, which occurred more frequently in patients receiving ondansetron plus dexamethasone (18.4% versus 8.1%, $p < 0.008$, and 8.9% versus 3.1%, $p < 0.035$, respectively).

The advantage of prochlorperazine is that, in addition to an oral and i.v. formulation, commercially available rectal and extended-release oral products may be an option in some patients. Two preliminary studies assessed the efficacy of

using the combination of metoclopramide, dexamethasone, and prochlorperazine for up to one week after cisplatin therapy. The treated groups had superior results to those of the control group.^{215,216} The combination of prochlorperazine, diphenhydramine, and lorazepam has also been shown to be effective.²¹⁷

Physiology of Radiation Therapy-Induced Nausea and Vomiting

Radiation therapy-induced emesis is a very complex process. The exact mechanism remains to be fully elucidated.^{11,218} It has been suggested that the vomiting center and the vagal nuclei, stimulated either directly by radiation or indirectly through chemical mediators, may play a critical role in producing the emetogenic effects of radiation.¹⁰ Possible chemical mediators include β -endorphin, prostaglandins, histamine, methionine, enkephalin, and catecholamines.^{10,11} Recently, it has been postulated that serotonin, released from the enterochromaffin cells of the GI tract, may induce vomiting through interactions with visceral afferent fibers and the 5-HT₃ receptors.²¹⁸

Factors to Consider in the Selection of an Agent for Radiation Therapy-Induced Nausea and Vomiting

Many patients receiving radiation therapy will require no medication for prevention or treatment of nausea and vomiting. In general, nausea and vomiting associated with radiation therapy is not as predictable or severe as chemotherapy-induced nausea and vomiting.

The site of radiation is a primary factor to consider in efforts to anticipate the risk, onset, peak, and duration of nausea and vomiting with radiation therapy. Essentially all patients who receive total body irradiation have nausea and vomiting, especially if radiation therapy is combined with highly emetogenic chemotherapeutic agents.⁸⁻¹² In contrast, the risk of emesis is low if only the extremities are irradiated.⁹ About 83% of patients receiving mid- and upper-hemibody irradiation have nausea and vomiting; the frequencies are 50% for fractionated radiation of the upper abdomen and 39% for lower-hemibody irradiation.^{9,219} With fractionated radiation of the upper abdomen, the onset is in two to three weeks. The onset is more rapid (40–90 minutes) with total body irradiation or mid-, upper-, or lower-hemibody irradiation.

Other radiation-related risk factors include the dose, dose rate, and field size (Table 8).⁸⁻¹² The risk of nausea and vomiting is greater if radiation is delivered as a single high dose than if it is given as fractionated smaller doses, if higher dose rates are used, and with larger field sizes (e.g., total body irradiation).^{11,219}

Chemotherapy given immediately before or concurrent with radiation therapy increases the risk of nausea and vomiting. Other factors include the psychological state of the patient (e.g., the presence of anxiety) and other stimuli, including smell, taste, and vestibular stimulation. Females are more apt to have nausea and vomiting than males, as are patients over the age of 10 years. Readers are referred to other resources for an overview of radiation therapy.^{9,11,220}

Studies of the management of nausea and vomiting in patients receiving radiation therapy are limited. Most of the studies are not well controlled. Determination of the most

Table 8.
Risk Factors for Radiation Therapy-Induced Emesis^a

<i>Treatment-Related Factors</i>	
Site of irradiation	
Dose of radiation	
Dose rate	
Field size	
<i>Other Factors</i>	
Recent or concurrent cytotoxic therapy	
Patient's psychological state	
Sensory stimuli	
Patient's sex	
Patient's age	

^aSee text for details.

appropriate antiemetic regimen is difficult because of the variability in design, patient selection, dosage regimen, irradiation treatment (site, dosage, duration), use of concomitant chemotherapy, definition of successful therapy, and variability in time course during which nausea and vomiting were assessed.

Prevention of Radiation Therapy-Induced Nausea and Vomiting

Recommendation 5. Patients receiving total or hemibody irradiation (with or without concomitant chemotherapeutic agents) or single-exposure, high-dose radiation therapy to the upper abdomen should receive preventive therapy for nausea and vomiting with each day of therapy. (Strength of evidence = A) A 5-HT₃ receptor antagonist should be used both in adults and in pediatric patients. (Strength of evidence = B) Oral therapy should be encouraged; however, i.v. therapy is an acceptable option. (Strength of evidence = B) There is no evidence to support the use of 5-HT₃ receptor antagonists 24 hours beyond the last dose of radiation.

Animal studies have demonstrated that, after irradiation, serotonin is released from the enterochromaffin cells of the intestine.³⁸ Emesis produced by radiation appears to be mediated through activation of peripheral or central 5-HT₃ receptors by the release of serotonin. 5-HT₃ receptor antagonists have been shown to be effective in alleviating radiation-induced emesis in ferrets.²²¹ Published studies support the efficacy of ondansetron, granisetron, and dolasetron for the prevention of emesis caused by radiation therapy.^{12,222-237} Frequently patients receive total body irradiation and chemotherapy concomitantly. Selection of an antiemetic agent should be based on both the level of emetogenicity of chemotherapy and risk factors associated with radiation-induced emesis. Readers are referred to Tables 6 and 7 for dosage regimens.

Ondansetron has been shown to be more effective than low-dose metoclopramide in patients undergoing radiation therapy. A multicenter, randomized, double-blind study compared oral ondansetron 8 mg with oral metoclopramide 10 mg in adult patients receiving 8 to 10 GY to the abdomen in a single exposure.²²⁴ Both medications were given one to two hours before radiation and every eight hours for five days. On day 1 of radiation, ondansetron was associated with complete control of emesis in 97% of the patients, compared with 46% of the patients treated with metoclopramide ($p < 0.001$). On days 2–5, the differences were no longer significant, with control in 68% and 65% of patients on days 2 and 3 with

ondansetron and metoclopramide, respectively, and 97% and 95% of patients on days 4 and 5 for ondansetron and metoclopramide, respectively. There are several limitations of the study. The dose of metoclopramide was low, the methods were not well described, and several other variables (e.g., concomitant medications or diseases, dose of radiation) could have influenced the results of the study.

Ondansetron was compared with prochlorperazine for the prevention of nausea and vomiting in 135 adults undergoing fractionated irradiation of the upper abdomen.²³⁵ Antiemetic therapy was administered throughout radiation therapy at the following dosages: ondansetron 8 mg orally three times daily and prochlorperazine 10 mg orally three times daily. Some 61% of the patients who received ondansetron and 35% of those given prochlorperazine had a complete response, with no emetic episodes throughout their treatment course ($p = 0.002$). One of the limitations of the study is the low doses of prochlorperazine used.

Prentice and colleagues²³⁷ compared i.v. granisetron with the combination of metoclopramide, dexamethasone, and lorazepam in 30 bone marrow transplant patients receiving total body irradiation. The patients in the granisetron group received a mean total radiation dose of 750 cGY and the combination-therapy group, 749 cGY; the doses were administered over a mean time of 1.2 hours in both groups. All patients had received chemotherapy, including high-dose cyclophosphamide, which was completed at least 66 hours before radiation therapy. After 24 hours, eight patients in the granisetron group and two in the combination-therapy group had a complete response.

In a double-blind, placebo-controlled trial, the efficacy of dolasetron 0.3, 0.6, and 1.2 mg i.v. for the prevention of nausea and vomiting after radiation therapy was examined.²³⁸ Significantly fewer patients in the placebo group than in the groups receiving 0.3, 0.6, or 1.2 mg had complete control of vomiting (54%, 100%, 93%, and 83%; $p = 0.002$).

If patients are able to take medication orally, therapy should be given by that route. This recommendation is based on potential therapeutic benefits, ease of administration, patient preference, and cost.

Limited evidence supports the use of the 5-HT₃ receptor antagonists during radiation therapy in the pediatric population.^{70,75,233,239,240} Most studies included children of various ages, and sometimes data in children were combined with data from adult patients. In an uncontrolled study by Jurgens and colleagues,²³¹ 15 children between the ages of two and seven years received undefined conditioning regimens of chemotherapy, total body irradiation, and ondansetron before bone marrow transplantation. Ondansetron was given intravenously at doses of 5 mg/m² or 8 mg immediately before the chemotherapy regimen, according to the body surface area. Intravenous or oral therapy at a dose of 2, 4, or 8 mg (according to body surface area) was continued three times daily during chemotherapy administration and total body irradiation and for a further two days if a noncisplatin conditioning regimen was used and five days if cisplatin was used. Complete or major control of emesis (zero to two emetic episodes) was achieved in 57% of the patients on their worst day of total body irradiation.

The 5-HT₃ receptor antagonist should be given with each day of radiation therapy. There is no evidence to support the use of 5-HT₃ receptor antagonists 24 hours beyond the last dose of radiation therapy.

Treatment of Radiation Therapy-Induced Nausea and Vomiting

Recommendation 6. If an agent is needed to treat established radiation therapy-induced emesis in adults, prochlorperazine, metoclopramide, or thiethylperazine is recommended. 5-HT₃ receptor antagonists are also an option. Chlorpromazine and lorazepam can be used in pediatric patients. (Strength of evidence = D)

Prochlorperazine, metoclopramide, and thiethylperazine have been used for the treatment of nausea and vomiting caused by radiation therapy.^{6,224,241,242} They are generally effective, have few adverse effects, and are available in different formulations—oral, injectable, and rectal (prochlorperazine only). Metoclopramide, although not commercially available as a rectal formulation, has been given rectally.²⁴³ The choice of agent should be based on anticipated adverse effects (Table 2), previous successes, and cost. If combination therapy is needed for severe nausea and vomiting, combination therapy should include medications with different mechanisms of action and adverse effect profiles. Patients should then receive prophylactic ondansetron or granisetron before each subsequent radiation treatment.

Treatments for nausea and vomiting secondary to radiation therapy in the pediatric population are not well substantiated. Recommendations to use chlorpromazine and lorazepam for treatment of radiation-induced nausea and vomiting are based on data from pediatric patients receiving the medications for treatment of nausea and vomiting secondary to other precipitating factors (e.g., chemotherapy).

Physiology of Postoperative Nausea and Vomiting

Many of the pathways in the control of postoperative nausea and vomiting are complex and have not been fully elucidated. With cancer chemotherapy-induced emesis, the agent is the stimulus. With postoperative nausea and vomiting, however, a wide range of stimuli contributes to the emetic response of patients.^{2,5,7,244-248}

Factors to Consider in the Selection of an Agent for Postoperative Nausea and Vomiting

Antiemetic selection should be based on safety and efficacy, patient factors, risk factors for nausea and vomiting, and costs. Many factors influence the risk and severity of postoperative nausea and vomiting (Table 9). They can be classified as pertaining to the patient, the operative procedure, anesthesia, or the postoperative period.

Certain patient characteristics increase the risk of postoperative nausea and vomiting.^{2,5,7,244-248} The risk is higher in adults than in children, in women (particularly premenopausal women) than in men, in obese patients, in patients who have a high level of preoperative anxiety, and in patients with a low threshold for nausea (e.g., patients with a history of motion sickness or patients who have previously had postoperative nausea and vomiting).^{5,244,246} The risk is also higher in patients with delayed gastric emptying secondary to disorders such as GI obstruction, gastroesophageal reflux disease, chronic cholecystitis, neuromuscular disorders, and intrinsic neuropathies.⁵ Gastric hypomotility

Table 9.
Risk Factors for Postoperative Nausea and Vomiting^a

<i>Patient-Specific Factors</i>
Age
Sex
Weight
Threshold for nausea
Psychological stress
Delayed gastric emptying
<i>Operative Procedure</i>
Indication for surgery
Type of surgery
Duration of procedure
Intubation procedure
<i>Anesthetic-Related Factors</i>
Preanesthetic medication
Oral intake
Gastric distension
Anesthetic
Reversal of muscle relaxation
Duration of anesthesia
Use of opioids
<i>Postoperative Factors</i>
Presence of pain
Patient movement
Oral intake

^aSee text for details.

can complicate conditions such as scleroderma, myotonic dystrophy, progressive muscular dystrophies, amyloidosis, and familial visceral myopathies.

The operative procedure also affects rates of postoperative nausea and vomiting.^{2,5,7,244-248} If nausea and vomiting are components of the disorder being treated (e.g., increased intracranial pressure, upper GI obstruction), the rate of postoperative nausea and vomiting may be increased.⁵ Certain types of procedures are associated with nausea and vomiting: intra-abdominal, major gynecological, orthopedic, ear–nose–throat, or laparoscopic surgery; adenotonsillectomy; and surgery for strabismus.^{5,7,244} Intubation may evoke nausea and vomiting, and longer procedures are associated with more nausea and vomiting than shorter ones.^{5,244}

Anesthesia-related factors must also be considered.^{2,5,7,244-248} The preanesthetic medication can influence the risk of postoperative nausea and vomiting. Morphine and other opioids can increase the risk; atropine decreases the risk.^{245,248} The risk of nausea and vomiting is generally less with regional nerve block procedures than with general anesthesia.⁵ General anesthetics vary in their propensity to cause postoperative nausea and vomiting. Etomidate and ketamine may increase the risk. Nitrous oxide and inhalation agents may also cause nausea, with the risk ranked as follows: ether and cyclopropane > halothane > enflurane > isoflurane > sevoflurane and desflurane. Propofol decreases the risk. Other factors that increase the risk of postoperative nausea or vomiting include a longer duration of anesthesia, the administration of opioids, the reversal of muscle relaxation, and gastric distension caused by suctioning or vigorous positive pressure ventilation via face mask. The presence of food in the stomach during induction of anesthesia increases the risk of nausea and vomiting both during induction and during the postoperative period.

During the postoperative period, nausea may be increased by sudden motion or changes in position or by unrelieved visceral or pelvic pain. Another factor is the timing of oral intake after surgery.^{5,247}

There is extensive literature addressing antiemetic selection for the prevention and treatment of postoperative nausea and vomiting. Although significant progress has been made over the years in the prevention of symptoms, patients continue to have difficulty with nausea and vomiting postoperatively. Vomiting can result in dehydration, electrolyte imbalance, prolongation of stay in the recovery room, hospital admissions, and loss of work. Although the data available to support agent selection is vast, the medications are difficult to compare because of the heterogeneity of the patient populations studied, small sample sizes, lack of consistency in definition of outcomes, and changes in anesthetic techniques over time.

Prevention of Postoperative Nausea and Vomiting

Recommendation 7. Patients who are at high risk of vomiting should receive antiemetic prophylaxis against postoperative nausea and vomiting. (Strength of evidence = C)

Not all surgical patients require medication for the prophylaxis of nausea and vomiting. Approximately 10% of patients will have symptoms in the recovery room and 30% will have symptoms for the first 24 hours after surgery.²⁴⁹ For some of these patients, the nausea is only transient. Administration of antiemetic medications, although considered generally safe, does place a patient at risk for adverse effects (Table 2). With some medications (e.g., metoclopramide, ondansetron), the dose of the antiemetic may be lower for prophylaxis of postoperative nausea and vomiting than chemotherapy-induced nausea and vomiting, and therefore adverse effects may be less common. The decision to provide antiemetic therapy should be based on the presence of risk factors for nausea and vomiting and the potential for serious sequelae from vomiting (e.g., head and neck surgery). A patient who has several risk factors (see Factors to Consider in the Selection of an Agent for Postoperative Nausea and Vomiting and Table 9) would be considered at high risk. Important factors contributing to a high risk of nausea and vomiting include the type of surgical procedure, history of motion sickness or postoperative nausea and vomiting, the patient's sex, and the administration of anesthetics known to cause the symptoms.

Propofol has been shown to decrease the frequency of nausea and vomiting in adults and children undergoing surgical procedures.^{250,251} A meta-analysis of 84 trials involving more than 6000 patients (of whom 3098 were treated with propofol) demonstrated that propofol does not have any clinically relevant antiemetic properties as an induction agent. When used for maintenance of anesthesia, propofol has relevant clinical effects (i.e., absence of nausea and vomiting) in the short term, when the potential for developing postoperative nausea and vomiting is greater than 20%.²⁵²

Recommendation 8. When prophylaxis is indicated, droperidol or a 5-HT₃ receptor antagonist is recommended for the prevention of postoperative nausea and vomiting in adult and pediatric patients. (Strength of evidence = A) Other medications that have been studied extensively and that are considered to be alternatives include chlorpromazine, prochlorperazine, metoclopramide, and promethazine. (Strength of evidence = B) Because droperidol and 5-HT₃ receptor antagonists are effective, the choice of agent

should be based on patient-specific factors and cost. Metoclopramide and prochlorperazine should generally not be used in pediatric patients. (Strength of evidence = C)

Efficacy of Droperidol. Droperidol is thought to exert its antiemetic properties by blocking dopamine receptors. Several trials have examined the efficacy of droperidol for the prophylaxis of postoperative nausea and vomiting in adults.²⁵³⁻²⁹⁶ A majority of trials that compared droperidol with placebo showed that the medication was effective in preventing nausea and vomiting in a variety of surgeries (e.g., gynecological, orthopedic, ophthalmic, cesarean section). Although efficacy was established when the drug was given before induction and at the end of surgery, better results were demonstrated when the medication was given intraoperatively.

Tables 10 and 11 show medications, dosages, and costs for antiemetics used for prophylaxis and treatment of nausea and vomiting postoperatively. Lower doses of droperidol (5–20 mg/kg) have been used successfully in procedures associated with a moderately high frequency of emesis (e.g., laparoscopy) but have limited efficacy for the more emetogenic procedures (e.g., surgery for strabismus). Higher doses of droperidol (2.5–5 mg in adults and 50–75 mg/kg in children) may be more effective in higher risk patients, although the patients should be monitored for adverse effects (e.g., sedation, dysphoria). Droperidol may cause restlessness and akathisia, which are of particular concern in outpatient surgeries.^{264,267,268,270,276}

Droperidol is generally well tolerated in the doses typically used for postoperative nausea and vomiting. Sedation is one of the most common adverse effects. Fortney et al.,²⁹⁶ in a large study of antiemetic prophylaxis in high-risk outpatients, found no significant differences among placebo, two dosages of droperidol, and ondansetron in terms of the occurrence of hypotension, sedation, or agitation and anxiety. In addition, patient satisfaction scores did not differ between the groups receiving one of the two dosages of droperidol and the ondansetron group. Dysphoria and akathisia reported by other investigators were not seen in this study. Mortensen²⁶⁰ found that, after minor gynecological surgery, significantly more patients who received droperidol were rated as excessively drowsy in recovery compared with placebo recipients but that there was no difference between placebo and droperidol recipients in duration of stay in the recovery ward. Extrapyramidal reactions rarely occur with droperidol in adults but may occur more frequently in pediatric patients.

Droperidol versus Metoclopramide. High doses (2 mg/kg) of metoclopramide have been used for chemotherapy-induced nausea and vomiting, but lower doses (0.1–0.2 mg/kg for adults and children) have been studied for the management of postoperative nausea and vomiting. Many of the studies of the efficacy and safety of metoclopramide for postoperative nausea and vomiting^{256,262,263,266,269,271,272,276,282-284,287,293,295,297-320} have yielded mixed results and involved diverse patient populations.^{262,266,271,272,276,289,293,295,300-302,308,309,312} Although most studies support the efficacy of metoclopramide, several studies in which droperidol was compared with metoclopramide showed significantly better results with droperidol.^{256,269,271,276,290,295}

In a randomized trial by DeSilva and colleagues,²⁹³ the prophylactic antiemetic efficacy of i.v. ondansetron, droperidol, perphenazine, and metoclopramide was com-

Table 10.
Standard Dosages and Costs of Antiemetics for Management of Postoperative Nausea and Vomiting in Adults

Agent	Dosage	Cost/Dose (\$) ^a
<i>Prophylaxis</i>		
Droperidol	0.625–1.25 mg i.v. 5 min before termination of anesthesia	0.43–0.86
Ondansetron	4 mg i.v. immediately before induction of anesthesia	24.45
	8 mg p.o. 1 hr before induction of anesthesia	38.46
Dolasetron	12.5 mg i.v. intraoperatively	18.60
	100 mg p.o. 1 hr before induction of anesthesia	66.00
Metoclopramide	10 mg i.v. given near end of procedure (20 mg may be used)	3.94–7.88
Promethazine	25 mg p.o. 1 hr before induction of anesthesia	0.04
	12.5–25 mg i.v. immediately before induction of anesthesia	0.28–0.55
Prochlorperazine	5–15 mg p.o. 1 hr before induction of anesthesia	0.54–1.62
	5–10 mg i.m. 1–2 hr before induction of anesthesia; may repeat once in 30 min if needed	1.10–2.20
	5–10 mg i.v. 15–30 min before induction of anesthesia; may repeat once as needed	1.10–2.20
Granisetron	20–40 µg/kg i.v.	243.54–487.08
<i>Treatment</i>		
Ondansetron	1–4 mg i.v. postoperatively	18.33–24.45
Metoclopramide	10 mg i.v. q 4–6 hr as needed postoperatively	3.94
Promethazine	10–25 mg p.o. q 4–6 hr as needed postoperatively	0.04
	12.5–25 mg i.m. or i.v. q 4 hr as needed postoperatively	0.28–0.55
Prochlorperazine	5–15 mg p.o. postoperatively	0.54–1.62
	5–10 mg i.m.; may repeat once in 30 min as needed	1.10–2.29
	5–10 mg i.v.; may repeat once as needed	1.10–2.20
Chlorpromazine	10–25 mg p.o. q 4–6 hr as needed	0.07–0.09
	12.5–25 mg i.m. if no hypotension; may repeat in 1 hr as needed	0.25–0.50
Droperidol	0.625–0.125 mg i.v. as needed	1.07–2.13
Dolasetron	12.5 mg i.v. postoperatively	18.73

^aCosts do not take into account waste that occurs when precise dosage forms are not available and reflect the February 1998 average wholesale price taken from the 1998 *Red Book*.

pared with that of placebo in 360 patients undergoing total abdominal hysterectomy. The patients had no organic disease or only mild to moderate systemic disease without functional impairment (a physical status score of I or II on the American Society of Anesthesiologists assessment scale). A significantly larger percentage of patients who received i.v. ondansetron, droperidol, or perphenazine were free of severe emetic episodes (63%, 76%, and 70%, respectively) compared with patients who received placebo. There was no significant difference between metoclopramide (50%) and placebo (43%). Patients who received droperidol or perphenazine had nausea scores that were significantly lower than the scores for placebo recipients ($p < 0.02$). Nausea scores of patients medicated with ondansetron or metoclopramide were not significantly different from those of placebo recipients.

Sedation, hypotension, and tachycardia are the most common adverse effects of droperidol (Table 2). The most common adverse effects of metoclopramide are sedation (up to 10%) and extrapyramidal effects. Intravenous administration has also resulted in hypotension, supraventricular tachycardia, and bradycardia.^{300,321–325} Neuroleptic malignant syndrome has been rarely reported with metoclopramide and droperidol.³²⁶

Efficacy of 5-HT₃ Receptor Antagonists. Placebo-controlled trials support the efficacy of ondansetron for the prevention of postoperative nausea and vomiting in adults^{293,327–355} and children.^{289,291,292,356–363} On the basis of these studies, ondansetron can be given as a single i.v. dose of 4 mg for adults and 0.05 mg/kg (range, 0.05–0.15 mg/kg) for children by slow i.v. injection at induction of anesthesia. A quantitative review of the literature by Tramer et al.²⁵² suggests that, for every 100 patients treated with ondansetron versus no prophylaxis for postoperative nausea and vomiting, 20 pa-

tients would not vomit. Ondansetron is the only 5-HT₃ receptor antagonist commercially available as an oral solution. Granisetron and dolasetron have been found to be stable over the short term in compounded suspensions.

Studies support the use of granisetron for the prevention of postoperative nausea and vomiting in adults and pediatric patients,^{364–373} although this medication has not been studied as extensively for this indication as ondansetron. Granisetron administered as a single i.v. dose of 20–40 mg/kg has been shown to be effective; however, a large-scale study supports the use of lower doses. Wilson and colleagues³⁷¹ compared the efficacy of three i.v. doses of granisetron (0.1, 1, and 3 mg) with that of placebo in a double-blind manner in 527 adults undergoing elective open abdominal surgery or vaginal hysterectomy during general anesthesia. Antiemetic prophylaxis with a single 1- or 3-mg i.v. dose of granisetron resulted in a significantly higher percentage of patients without emetic episodes (63% with 1 mg and 62% with 3 mg) than with placebo (34%, $p < 0.001$). A significantly greater percentage of patients achieved total control during the postoperative periods of 0–6 and 0–24 hours.

Randomized, double-blind, placebo-controlled, dose-ranging studies show the efficacy and safety of i.v. and oral dolasetron in preventing postoperative nausea and vomiting.^{374–381} A pivotal randomized, double-blind study by Graczyk and colleagues³⁷⁴ assessed the efficacy and safety of single i.v. doses of dolasetron 12.5, 25, and 50 mg compared with placebo in 635 patients undergoing outpatient gynecological surgery. Dolasetron or placebo was given 15 minutes before the end of anesthesia. Efficacy was determined by evaluating the percentage of patients who had a complete response (no episodes of vomiting and no doses of rescue antiemetics for 24 hours after recovery). All three i.v. doses of dolasetron were superior to placebo in prevent-

Table 11.
Standard Dosages and Costs of Antiemetics
for Management of Postoperative Nausea and
Vomiting in Pediatric Patients

Agent	Dosage	Cost/Dose (\$) ^a
<i>Prophylaxis</i>		
Dolasetron	>2 yr old: 1.8 mg/kg i.v. immediately before induction	53.95
Ondansetron	0.05 mg/kg i.v. (range, 0.05–0.15 mg/kg)	18.33
Droperidol	0.015–0.075 mg/kg/dose i.v.	1.38–6.88
<i>Treatment</i>		
Chlorpromazine	0.55 mg/kg p.o. or i.m.	10.22
Droperidol	0.1 mg/kg/dose i.v.	1.38
Ondansetron	0.05 mg/kg/dose i.v.	18.33

^aFor a 20-kg child and taken from the 1998 *Red Book*.

ing postoperative nausea and vomiting ($p < 0.0003$). The complete response rates were 50.3%, 51.6%, and 55.6%, respectively, for the 12.5-, 25-, and 50-mg dolasetron doses, compared with 30.6% for placebo. Of the doses tested, 12.5 mg was the lowest maximally effective dose.

The sole comparative trial of dolasetron for postoperative nausea and vomiting was a randomized double-blind, placebo-controlled comparison of dolasetron 25 or 50 mg i.v. and ondansetron 4 mg i.v. in 514 patients.³⁷⁵ Patients received placebo or one of the three antiemetic regimens upon induction of anesthesia. Efficacy was measured by the rate of complete response to antiemetic therapy (no emesis or use of rescue medications) and total response (complete response plus no nausea). Complete and total response rates were higher for dolasetron 50 mg i.v. and ondansetron 4 mg i.v. than for dolasetron 25 mg i.v. or placebo. Complete response rates were 71% for dolasetron 50 mg, 64% for ondansetron 4 mg, 51% for dolasetron 25 mg, and 49% for placebo. The authors concluded that dolasetron 50 mg i.v. was equivalent to ondansetron 4 mg i.v., given at the induction of anesthesia, for prevention of postoperative nausea and vomiting. The dose of dolasetron used was four times the FDA-approved dose of 12.5 mg given intraoperatively.

Dolasetron has not been studied for the prevention of postoperative nausea and vomiting in pediatric patients. Therefore, the appropriate dose is unknown. For preventing nausea and vomiting secondary to chemotherapy in pediatric patients, doses of 1.8 mg/kg have been used.

The antiemetic efficacy of ondansetron 4 mg, tropisetron 5 mg, granisetron 3 mg, metoclopramide 10 mg, and placebo was examined in a prospective, randomized double-blind trial in 132 patients undergoing cholecystectomy.³⁷⁰ For the 24-hour recovery period after surgery, the percentages of emesis-free patients were 65% for ondansetron, 52% for tropisetron, 48% for granisetron, 29% for metoclopramide, and 28% for placebo. The three 5-HT₃ receptor antagonists did not differ significantly in efficacy.

Prevention of nausea and vomiting with oral dolasetron has been studied in two randomized, double-blind, placebo-controlled trials.^{380,381} Warriner et al.³⁸¹ and Diemunsch et al.³⁸⁰ used nearly identical study designs. Both studied dolasetron in oral doses of 25, 50, 100, and 200 mg given before the induction of anesthesia. One study enrolled 373 patients³⁸¹ and the other, 789 patients.³⁸⁰ Complete response was defined in both trials as no vomiting or use of

rescue medication for 24 hours postoperatively. Warriner et al. reported that only the 100- and 200-mg oral doses of dolasetron were superior to placebo in terms of the percentage of complete responses (54.1% for 100 mg and 49.35% for 200 mg; $p < 0.003$ and $p < 0.01$, respectively, versus placebo [29.3%]). In the study by Diemunsch et al., complete response rates were higher for dolasetron 50, 100, and 200 mg (>47%) than for placebo (35%) or dolasetron 25 mg (45%). No increase in efficacy was seen at doses greater than 50 mg. These two trials collectively support the use of oral dolasetron 100 mg to prevent postoperative nausea and vomiting.

The 5-HT₃ receptor antagonists are generally well tolerated, with headache being the most frequently occurring effect.

Droperidol versus the 5-HT₃ Receptor Antagonists. Fortney et al.²⁹⁶ randomly assigned more than 2000 patients at high risk for developing postoperative nausea and vomiting to receive placebo, droperidol 0.625 mg, droperidol 1.25 mg, or ondansetron 4 mg i.v. before the induction of anesthesia. The patients received a standard induction with a barbiturate and were allowed to receive midazolam, fentanyl, or alfentanil as premedication. All three of the treatments were superior to placebo in terms of complete responses at 0–2 hours postoperatively (droperidol 0.625 mg, 63%; droperidol 1.25 mg, 69%; ondansetron 4 mg, 62%; placebo, 46%) and 24 hours postoperatively (48%, 56%, 53%, and 35%, respectively). Ondansetron 4 mg was equivalent to droperidol 0.625 mg in terms of the number of complete responses at 0–2 hours (63% versus 62%), and droperidol 1.25 mg was superior to ondansetron 4 mg at 0–2 hours (69% versus 62%). All three treatment groups had similar efficacy in the 0–24 hours postoperatively. Headache was more frequent among the ondansetron-treated patients than the droperidol-treated patients. There were no significant differences among the treatment groups with regard to the frequency of hypotension, sedation, or agitation and anxiety. Patient satisfaction scores were similar for all treatment groups.

Results were mixed when droperidol was compared with ondansetron in adult surgical patients. Some studies showed no difference in the frequency of nausea and vomiting.^{290,293,346,382} Alon and colleagues^{282,383} did not find a difference in the frequency of vomiting but found that droperidol prevented nausea to a greater degree than ondansetron. In the study by Paxton and colleagues,³⁵¹ at one, two, and four hours after surgery, the scores for nausea were significantly lower in the ondansetron group than in the groups receiving metoclopramide, droperidol, or placebo; thereafter, there was no significant difference between the groups. All medications were given before induction of anesthesia. Two investigators reported that droperidol was superior to ondansetron.^{294,383}

In a large-scale placebo-controlled study by Tang and colleagues,³⁸⁴ ondansetron 4 mg i.v. was compared with droperidol 0.625 or 1.25 mg i.v. for the prevention of nausea and vomiting associated with outpatient gynecological surgery. The frequency of nausea and vomiting, times to achieve recovery, and patient-evaluated scores on visual-analogue scales for sedation, anxiety, pain, and nausea were recorded along with postdischarge emetic episodes, medications, quality of sleep, time to resumption of food intake and normal activity, and time to return to work. The frequency of nausea and vomiting in the hospital and after discharge, the need for rescue antiemetic therapy, and recovery and dis-

charge times were similar for both droperidol groups and the ondansetron group, but these groups differed significantly from the placebo group. The cost-effectiveness ratios for both droperidol groups were significantly lower than those for the ondansetron and placebo groups. The authors concluded that droperidol 0.625 mg i.v. is comparable to ondansetron 4 mg i.v. for the prevention of emesis without increasing adverse effects or delaying discharge and is more cost-effective.

Watcha and Smith³⁸⁵ compared the cost-effectiveness of ondansetron, droperidol, and metoclopramide in the prevention of postoperative nausea and vomiting. The total incremental costs associated with prophylactic ondansetron, metoclopramide, and droperidol were \$37.74, \$28.43, and \$18.17 per patient, respectively. For ondansetron, prophylactic use was cost-effective only when the frequency of emesis exceeded 33%, whereas prophylactic droperidol was cost-effective even when the frequency was as low as 10%.

Droperidol has been compared with ondansetron for the prevention of postoperative nausea and vomiting in pediatric patients, with mixed results.^{286,288,289,291,292,386} One of the studies found ondansetron to be significantly more effective than droperidol²⁸⁹; the other five studies found no significant difference between the two agents.^{286,288,291,292,292,386} However, many of these studies did not have a sufficient sample size to allow a significant difference to be detected.^{286,288,291} Lawhorn and colleagues²⁸⁶ demonstrated that ondansetron provides antiemetic control for up to 24 hours; droperidol lasts for a significantly shorter period.

Fujii et al.^{372,387} compared the efficacy of droperidol with that of granisetron. In one study,³⁸⁷ 80 patients scheduled for elective laparoscopic cholecystectomy were randomly assigned to receive placebo, droperidol 1.25 mg i.v., or granisetron 3 mg i.v. administered before induction of anesthesia. Nausea and vomiting occurred in 46% of placebo recipients, 41% of patients who received droperidol, and 15% of patients who received granisetron ($p < 0.05$). Four patients in the placebo group, two in the droperidol group, and none in the granisetron group required rescue therapy. The dose of granisetron was four times higher than doses used to prevent nausea and vomiting in patients receiving chemotherapy. In another trial, Fujii et al.³⁷² compared granisetron 40 mg/kg, droperidol 1.25 or 2.5 mg, and placebo in 100 patients undergoing gynecological surgery. The efficacy of granisetron in preventing nausea and vomiting was similar to that of droperidol 2.5 mg. In this study, a higher dose of droperidol and a lower dose of granisetron were used. Although granisetron is effective for the prevention of postoperative nausea and vomiting, the optimal dose is unknown.

Other Antiemetic Agents. Other agents have been tested for their efficacy in the prevention and treatment of postoperative nausea and vomiting, but studies are limited in number and quality. Representative agents include prochlorperazine,^{257,388-390} cyclizine,³⁹¹⁻³⁹⁵ benzquinamide,³⁹⁶⁻³⁹⁹ dronabinol,⁴⁰⁰ trimethobenzamide,^{401,402} dimenhydrinate,⁴⁰³ thiethylperazine,^{404,405} chlorpromazine,^{403,406-410} promethazine,^{281,388,408} haloperidol,^{257,317,318,411} ephedrine,^{283,412} clonidine,³⁷³ hydroxyzine,^{260,413} perphenazine,^{293,319,320,395,401,403,414-417} dexamethasone,^{372,417} and midazolam.⁴¹⁸

In October 1997, FDA approved a scopolamine patch (Transderm Scop, Novartis) for the prevention of nausea and vomiting related to anesthesia and some pain relievers used during or after surgery. The most common adverse effects

associated with use of the patch are dry mouth and visual disturbances.⁴¹⁹ Large-scale clinical trials to compare scopolamine with droperidol or 5-HT₃ receptor antagonists in a variety of populations need to be completed so that the role of this medication in the management of postoperative nausea and vomiting can be better defined.

Treatment of Postoperative Nausea and Vomiting

Recommendation 9. Droperidol or 5-HT₃ receptor antagonists are recommended for adult and pediatric patients with established postoperative nausea and vomiting. (Strength of evidence = A) Other medications that have been studied extensively and that are considered to be alternatives include chlorpromazine, prochlorperazine, and promethazine. (Strength of evidence = B) The choice of agent should be based on patient-specific factors and cost. Prochlorperazine and metoclopramide should generally not be used in pediatric patients.

When ondansetron is used to treat postoperative nausea and vomiting, doses of 1–4 mg i.v. are effective.^{344,345,420,421} In a study by Scuderi and colleagues,³⁴⁴ 500 surgical patients undergoing endotracheal anesthesia received 1, 4, or 8 mg of ondansetron or placebo in a randomized, double-blind fashion in response to nausea or vomiting. Complete response to therapy (0–2 hours) was found in 57%, 61%, and 57% of the patients receiving 1, 4, and 8 mg, respectively, which was significantly better than the complete response rate in the placebo group (30%, $p < 0.001$). For the 0- to 24-hour period, the complete response rate was 15% in the placebo group and 41%, 47%, and 47%, respectively, in the groups receiving ondansetron 1, 4, and 8 mg. A typical dose for pediatric patients is 50 mg/kg.

Dolasetron i.v. was evaluated for the treatment of established postoperative nausea and vomiting in several studies.^{376,378,402,422,423} Diemunsch et al.³⁷⁶ and Kovac et al.³⁷⁸ used similar randomized, double-blind study designs and methods to assess the efficacy and safety of dolasetron 12.5, 25, 50, and 100 mg i.v. and placebo in more than 1000 predominantly female patients during the 24-hour period after surgery. In both studies, patients were enrolled after experiencing at least one episode of moderate to severe postoperative nausea or vomiting lasting more than five minutes in the 2-hour period after surgery.

Kovac et al. reported that the percentage of patients with complete responses was significantly higher with dolasetron (all doses) than with placebo at 2 and 24 hours ($p < 0.05$). The 12.5-mg dose was as effective as 25, 50, and 100 mg after 24 hours (complete response rate of 35%, versus 28%, 29%, and 29%, respectively). Nausea scores were significantly lower in patients treated with dolasetron 25 and 100 mg than in the placebo group ($p < 0.05$).

Diemunsch and colleagues³⁷⁶ reported that all four dolasetron groups had higher complete response rates after 24 hours than the placebo group ($p < 0.05$). The group receiving 50 mg had the highest complete response rate (37.3%); response rates for the 12.5-, 25-, and 100-mg groups were 24.2%, 27.7%, and 25.0%, respectively.

Because of the inconsistency in findings between Kovac et al.³⁷⁸ and Diemunsch et al.,^{376,422} Watkins et al.³⁷⁹ combined the data from the two trials to attempt to make a more concrete recommendation for the safest and most effective dose to employ in the treatment of established postoperative nausea or vomiting. In the pooled analysis, all i.v. doses of dolasetron were more efficacious than placebo

in terms of complete response ($p < 0.003$) and antinausea effects ($p < 0.027$). Patterns of adverse events were similar with placebo and all doses of dolasetron. The investigators concluded that the overall efficacy of dolasetron did not increase with higher doses, and the dose of 12.5 mg i.v. was recommended for use in treating established nausea or vomiting postoperatively.

Dolasetron has not been studied for the treatment of postoperative nausea and vomiting in pediatric patients.

Managing Patients Who Are Unresponsive to Prophylactic Antiemetic Therapy

Recommendation 10. When patients do not respond to initial therapy with an antiemetic agent, it is recommended that an agent from another pharmacologic class be added, that the dose of the antiemetic be increased to the maximum within an accepted range, or that a combination of both approaches be used. (Strength of evidence = D)

Evidence suggesting how to manage patients who do not respond to prophylactic antiemetics during the first cycle of chemotherapy, during radiation therapy, or after surgery is limited. In these circumstances, the patients undergoing chemotherapy or radiation therapy should receive rescue antiemetic agents as treatment. Postoperatively and for patients scheduled to receive their next cycle of chemotherapy or radiation therapy, an agent from another pharmacologic class can be added, the dose of the antiemetic may be increased to the maximum within the accepted range (increasing the dose of i.v. ondansetron from 8 to 16 mg for chemotherapy-induced nausea and vomiting or up to 4 mg for postoperative nausea and vomiting), or a combination of both approaches may be used. There is no documented benefit to further increasing the dose once the maximum dose has been reached in the accepted range (e.g., ondansetron 32 mg for chemotherapy-induced nausea and vomiting, 8 mg for postoperative nausea and vomiting). The maximum is generally the FDA-approved dose. An exception to this may be postoperative use of ondansetron 8 mg.

Conclusion

Appropriate management of nausea and vomiting in adult and pediatric patients receiving chemotherapeutic agents or radiation therapy or undergoing surgery has the potential to substantially improve clinical, humanistic, and economic outcomes.

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Recommendations

1. The emetic potential of the chemotherapeutic agent (Table 3) is the primary factor to consider when deciding whether to administer pharmacologic prophylaxis and which antiemetic(s) to select. (Strength of evidence = A)
2. Adult and pediatric patients receiving chemotherapeutic agent(s) with emetic potential classified as level 2 through 5 should receive pharmacologic prophylaxis against nausea and vomiting each day on which chemotherapy is given. (Strength of evidence = B) Antiemetic prophylaxis is not required when the level of emetogenicity is 1.
 - (a) Adult and pediatric patients receiving level-2 chemotherapeutic regimens can receive dexamethasone or methylprednisolone alone for prophylaxis of nausea and vomiting. (Strength of evidence = B) Prochlorperazine is also an option for adults. (Strength of evidence = D)
 - (b) Adult and pediatric patients receiving chemotherapeutic agent(s) with emetic potential of level 3 through 5 should receive a corticosteroid (dexamethasone or methylprednisolone) in combination with a 5-HT₃ receptor antagonist. (Strength of evidence = A for adults and C for pediatric patients)
 - (c) Orally and intravenously administered antiemetics are generally equivalent in efficacy and safety for both adult and pediatric patients. (Strength of evidence = B for adults and C for pediatric patients) The decision as to which formulation to use should be based on patient-specific factors and cost.
 - (d) The decision as to which 5-HT₃ receptor antagonist to use should be based on the acquisition cost of comparable doses. (Strength of evidence = A) (Tables 6 and 7) Dosage recommendations for adult and pediatric patients differ.
3. All patients receiving chemotherapy should have antiemetics available on an as-needed basis for rescue for breakthrough nausea and vomiting. (Strength of evidence = A) Patients should be educated on the appropriate administration of and expectations for therapy and should be reassured that every effort is being made to prevent symptoms. In adults, lorazepam, methylprednisolone, prochlorperazine, metoclopramide, dexamethasone, haloperidol, and dronabinol are effective. (Strength of evidence = C) In pediatric patients, chlorpromazine, lorazepam, or methylprednisolone (or dexamethasone) is recommended. (Strength of evidence = B) The choice of agent should be based on patient-specific factors (e.g., anticipated adverse effects, past success) and cost.
4. For the prevention of delayed emesis after cisplatin therapy in adults, dexamethasone with metoclopramide or a 5-HT₃ receptor antagonist is recommended. (Strength of evidence = A) The choice of agent should be based on patient-specific factors and cost. For delayed emesis after cyclophosphamide, doxorubicin, or carboplatin therapy, a 5-HT₃ receptor antagonist with dexamethasone is recommended. (Strength of evidence = B) Prochlorperazine in combination with dexamethasone has also been used and is available in extended-release and rectal dosage forms, but the evidence to support this combination is limited. (Strength of evidence = D) In pediatric patients, chlorpromazine, lorazepam, or a 5-HT₃ receptor antagonist can be used in combination with a corticosteroid. (Strength of evidence = C)
5. Patients receiving total or hemibody irradiation (with or without concomitant chemotherapeutic agents) or single-exposure, high-dose radiation therapy to the upper abdomen should receive preventive therapy for nausea and vomiting with each day of therapy. (Strength of evidence = A) A 5-HT₃ receptor antagonist should be used both in adults and in pediatric patients. (Strength of evidence = B) Oral therapy should be encouraged; however, i.v. therapy is an acceptable option. (Strength of evidence = B) There is no evidence to support the use of 5-HT₃ receptor antagonists 24 hours beyond the last dose of radiation.
6. If an agent is needed to treat established radiation therapy-induced emesis in adults, prochlorperazine, metoclopramide, or thiethylperazine is recommended. 5-HT₃ receptor antagonists are also an option. Chlorpromazine and lorazepam can be used in pediatric patients. (Strength of evidence = D)
7. Patients who are at high risk of vomiting should receive antiemetic prophylaxis against postoperative nausea and vomiting. (Strength of evidence = C)
8. When prophylaxis is indicated, droperidol or a 5-HT₃ receptor antagonist is recommended for the prevention of postoperative nausea and vomiting in adult and pediatric patients. (Strength of evidence = A) Other medications that have been studied extensively and that are considered to be alternatives include chlorpromazine, prochlorperazine, metoclopramide, and promethazine. (Strength of evidence = B) Because droperidol and 5-HT₃ receptor antagonists are effective, the choice of agent should be based on patient-specific factors and cost. Metoclopramide and prochlorperazine should generally not be used in pediatric patients. (Strength of evidence = C)
9. Droperidol or 5-HT₃ receptor antagonists are recommended for adult and pediatric patients with established postoperative nausea and vomiting. (Strength of evidence = A) Other medications that have been studied extensively and that are considered to be alternatives include chlorpromazine, prochlorperazine, and promethazine. (Strength of evidence = B) The choice of agent should be based on patient-specific factors and cost. Prochlorperazine and metoclopramide should generally not be used in pediatric patients.
10. When patients do not respond to initial therapy with an antiemetic agent, it is recommended that an agent from another pharmacologic class be added, that the dose of the antiemetic be increased to the maximum within an accepted range, or that a combination of both approaches be used. (Strength of evidence = D)

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